

# American Journal of Obstetrics and Gynecology

VOL. 56

NOVEMBER, 1948

No. 5

## Original Communications

### DIETHYLSTILBESTROL IN THE PREVENTION AND TREATMENT OF COMPLICATIONS OF PREGNANCY\*

O. WATKINS SMITH, PH.D., BROOKLINE, MASS.†

(From the Fearing Research Laboratory, Free Hospital for Women)

THE present study, a clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy, was started in the fall of 1943 and is still in progress.‡ To date complete reports upon 632 pregnancies have been received and analyzed at the Fearing Research Laboratory. Both ward and private patients are represented, although the majority were private. The writer would like to emphasize that the credit for the present contribution belongs to the 117 obstetricians who not only followed our recommendations but were willing to pool their results and to send to us a complete record of each treated case.§ Some had sufficient material for a personal communication (D. Abramson, Boston, Mass.; L. Woods and W. Calden, Oakland, Cal.; P. Gustafson, Boston, Mass.; G. Heels, Cambridge, Mass.; C. L. Sullivan and R. J. Heffernan, Boston, Mass.; and H. B. Nelson, Boston, Mass.). The pooled results are, of course, very much more significant than

\*Presented before the Norfolk District Medical Society, Boston, Mass., Feb. 24, 1948.

†With the collaboration of 117 obstetricians from 48 cities and towns in New York, New Jersey, Pennsylvania, District of Columbia, Illinois, North Carolina, Virginia, Texas, New Mexico, California, and all of the New England States.

‡E. R. Squibb & Sons has supplied 25 mg. tablets of stilbestrol for most of the cases treated.

§In order to be certain of procuring a record on every treated patient, each doctor, upon receiving an allotment of stilbestrol, was required to send in a card for each patient to be treated, stating the name of the patient, the last menstrual period, and the indication for therapy. These cards were filed under the doctor's name according to the expected date of confinement. Final record sheets were also supplied and, if not returned soon after a patient was due to deliver, follow-up letters were sent to the obstetrician. In this way we hoped to be sure of receiving records on all treated patients and to overcome the tendency of any busy practitioner to forget short periods of therapy that terminated in failure. We believe we have been fairly successful in this, since our only incomplete records to date are on patients who moved away in the middle of a pregnancy and could not be traced by their obstetricians. There is the possibility, however, that cards were not sent in on all cases. In tabulating the data, however, we have analyzed all past pregnancies of these patients, and used this means of evaluating results. It would seem that the significance of any differences noted between treated pregnancies and the untreated complications of the same group of patients would not be materially diminished by lost cases.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

the individual reports of much smaller series would have been, particularly since they represent a cross section of climatic conditions, dietary variations, geographic distribution, and general obstetric care throughout the United States.

### **Basis for the Use of Diethylstilbestrol in Pregnancy**

The observation that a marked rise in estrogen excretion at about the tenth to twelfth week of normal pregnancy was followed by an equally marked drop in chorionic gonadotropin (C.G.) was reported by Smith and Smith in 1936.<sup>1</sup> In 1938 the same phenomenon was observed following estrogen administration to pregnant women.<sup>2</sup> Their quantitative studies of estrogens, pregnanediol, and serum C.G. in pregnancy suggested to them that an abnormal rise in serum C.G. might reflect failing utilization of this factor for the production of the placental steroids.<sup>2,3</sup> Since studies in both pregnant and nonpregnant women had indicated that a rise in estrogen always preceded any increased secretion of progesterone, it was logical to propose that estrogens were in some way causally related to corpus luteum activity in the nonpregnant women and to the utilization of C.G. in pregnancy for the placental production of progesterone. The results of experiments by Heckel and Allen in 1939<sup>4</sup> lent support to this idea by demonstrating that progesterone secretion could be maintained and delivery postponed in the pregnant rabbit by estrogen administration. In 1941 Smith and Smith<sup>5</sup> summarized their findings on estrogen and progesterone metabolism in women, and concluded from the results that estrogen oxidation products rather than estrogens per se were responsible for the progesterone stimulating effect of estrogen, through pituitary stimulation in nonpregnant women<sup>6</sup> and through causing increased utilization of C.G. in pregnancy.<sup>5</sup> It was demonstrated experimentally that progesterone, which depresses the rate of estrogen oxidation, also markedly inhibited the pituitary stimulating properties of estrone.<sup>7</sup> In any attempt to enhance progesterone secretion with estrogens in human pregnancy, therefore, more estrogen would have to be given than could be metabolized by the available progesterone.<sup>8</sup> It was found, however, that diethylstilbestrol, unlike the naturally occurring estrogens, was not depressed in its pituitary stimulating effects by the presence of progesterone<sup>9</sup> and might theoretically, therefore, provide an ideal agent for preventing progesterone deficiency in pregnancy. Experimental support of the concept that stilbestrol would enhance the utilization of C.G. for the production of progesterone had been supplied by the finding that this estrogenic compound augmented the ovarian response of hypophysectomized rats to C.G. resulting in corpus luteum formation, an effect which cannot be achieved in the hypophysectomized animal either by C.G. or stilbestrol alone.<sup>10</sup>

More direct support of the concept was supplied by the results of quantitative assays for urinary pregnanediol and serum C.G. in two diabetic women with bad obstetric histories to whom stilbestrol was being administered as a preventive measure against late pregnancy accidents.<sup>11,12</sup> A rise in urinary pregnanediol and a drop in serum C.G. was noted upon the initiation of stilbestrol therapy, whereas a reversal of this effect occurred each time that the drug was experimentally discontinued. This observation has been repeatedly confirmed in a series of patients with bad obstetric histories who are now being followed at the Boston Lying-in Hospital. So far as our present knowledge takes us, therefore, the concept seems tenable that stilbestrol causes an increased secretion of progesterone in human pregnancy (probably by the placental syncytium) through causing an increased



utilization of C.G. An important part of the understanding of this concept is the realization that stilbestrol is given not because it is estrogenic but because it stimulates the secretion of estrogen and progesterone. The dosages prescribed are not enough per se to raise the estrogen level above the physiologic norm of pregnancy (v.i.). It may be assumed, therefore, that any effect that stilbestrol has in these dosages is through its ability to stimulate a greater production of the placental steroid hormones rather than through its estrogenic activity.

### Indications for Stilbestrol Therapy in Pregnancy

If the above concept is correct stilbestrol should prove beneficial in any abnormal situation of pregnancy in which progesterone deficiency may be etiologically involved, *provided the cells which secrete the steroid hormones are still capable of functioning.* That progesterone deficiency might result in abortion, miscarriage, and premature delivery has been assumed since 1929, when the classical investigations of Corner and Allen on the physiologic properties of the corpus luteum hormone were published.<sup>13</sup> That a progressive deficiency of the steroid hormones invariably precedes the onset of late pregnancy toxemia, eclampsia, premature delivery and intrauterine death has been shown by the investigations of Smith and Smith.<sup>5</sup> It has been repeatedly pointed out by them, moreover, that a reciprocal relationship exists between the vascular supply to the placenta and the circulating level of steroid hormones, adequate vascularity being essential for the normal production and metabolism of estrogen and progesterone and adequate hormonal supply being equally essential for vascular development in the pregnant uterus. On this basis, they have never felt that the primary abnormality responsible for late pregnancy complications was necessarily hormonal, but they are of the opinion that this deficiency is always a contributory factor to the final syndrome which precipitates the clinical manifestations.<sup>14</sup> By combating this hormonal deficiency it was hoped that stilbestrol, even in such conditions as essential hypertension and twin pregnancy where the primary deficiency is almost certainly of maternal vascular origin rather than hormonal, would postpone the onset, lessen the severity, and possibly reduce the incidence of later pregnancy complications. The use of stilbestrol alone as a definitive measure for the treatment of late pregnancy toxemia, as opposed to its prophylactic use, is not recommended by them because of their evidence that the onset of clinical signs reflects syncytial degeneration, toxin formation, and vascular damage so advanced that increased secretion of progesterone cannot be stimulated.<sup>12</sup>

### Dosage

The dosage schedule proposed by the Smiths, and which has been followed by most of the obstetricians who contributed to the present study, is based upon their quantitative determinations of hormonal levels throughout normal pregnancy, and is planned to approximate physiologic conditions as closely as possible.\* Five milligrams daily by mouth is started during the sixth or seventh week (counting from the start of the last menstrual period). The daily

\*The average daily estrogen excretion of women during normal pregnancy, if expressed in milligrams of estradiol plus estrone plus estriol, has been found to increase from about 0.5 mg. at eight to twelve weeks to 40 mg. at thirty-eight weeks. At thirty-six weeks, when we advise the cessation of stilbestrol therapy, the average excretion is about 15 to 20 mg. Recovery experiments in women have indicated that no more than 10 per cent of administered estrogen is excreted early in pregnancy and no more than 15 per cent during the last trimester. Excretion, therefore, may be assumed to represent about these percentages of the amount originally formed. Our dosage schedule of 5 mg. of stilbestrol at six or seven weeks increasing to 125 mg. during the thirty-sixth week, therefore, should approximate the average level of production. This means that the level of circulating estrogens in an average normal woman (assuming that all the stilbestrol taken orally was absorbed) might conceivably be doubled. Even if such complete absorption occurred, which is unlikely, the level of estrogen of any patient on our schedule would still be within the range of normal, since there is such a wide variation in normal women.

dosage is increased by 5 mg. at two-week intervals to the fifteenth week when 25 mg. daily are being taken. Thereafter, the daily dosage is increased by 5 mg. at weekly intervals. Administration is discontinued at the end of the thirty-fifth week since a drop in estrogen and progesterone normally precedes the onset of labor. For the prevention of late pregnancy accidents stilbestrol is started as early as possible, but no later than the sixteenth to nineteenth week, since a deficiency of estrogen oxidation products has been demonstrated during the second trimester in these patients.<sup>8</sup> The initial dosage is always the one for the particular week of pregnancy when therapy is begun.

### Clinical Results

The case reports have been divided according to the indications for stilbestrol therapy.

*Stilbestrol for threatened abortion.*—(Table I.) In this group are included only patients who were bleeding, with or without cramps, between the sixth and twenty-first weeks of pregnancy. Although the amount of bleeding was not specified in many of the cases, it was described as definite bleeding as opposed to staining. Bleeding at about the time of the first missed period was not considered threatened abortion, since endometrial bleeding at the site of implantation has been shown to occur normally and might well be sufficient to result in outside bleeding at this time.<sup>15</sup> Thirty-four patients whose only symptom was cramps are also omitted from this group (32 of these, or 94 per cent, carried) but many of them had had previous abortions, and are therefore included in Table II.

TABLE I. STILBESTROL FOR ABORTION; DEFINITELY FOR THREATENED ABORTION (BLEEDING 6 OR 8 CRAMPS WKS. 6-21); 219 CASES\*

PREVIOUS ABORTIONS	NO. OF CASES	CARRIED TO 28 WEEKS (PER CENT)	LIVING AND WELL BABIES (PER CENT)
0	143	74	70
1	46	88	77
2	17	82	72
3 or more	13	83	82
Total	219	78	72

\*Including 9 cases on too low dosage, 6 of whom aborted and 15 cases on too high dosage, 4 of whom aborted.

Seventy-eight per cent of the 219 women carried to twenty-eight weeks, and 72 per cent obtained living children. Hertig and Livingstone,<sup>16</sup> in reviewing the literature on this subject, concluded that approximately 40 per cent of threatened abortions do not abort regardless of treatment. The highest spontaneous cure rate that they quote from the literature is 50 per cent. Since the cases reported in Table I received no supplementary therapy other than bed rest and sedation, the increased salvage must have been due to stilbestrol and is highly significant.\* Twenty-two of the abortuses were examined pathologically and 17, or 77 per cent, were found to be defective. There were no abnormalities in the fetuses that were carried.† It is note-

\*Throughout this communication the difference between our observed incidence of any abnormality and the incidence in a control series is considered significant only if it could occur by chance no more than once in 80 times, i.e.,  $\text{Deviation} \div \text{Standard Deviation}$  equals 2.5 or more.

†On the basis of the pathologic examination of 1,000 abortuses, Hertig<sup>16</sup> has postulated a theoretically possible salvage rate of 60 per cent, assuming that 40 per cent of these would carry regardless of treatment. The higher salvage in these 219 patients who received stilbestrol suggests that perhaps Hertig placed the spontaneous cure rate too low. If the spontaneous cure rate is placed at 50 per cent, the highest figure reported, then the theoretically possible salvage rate becomes 70 per cent on the basis of Hertig's observations. A 78 per cent salvage in 219 cases is not significantly greater than 70 per cent.

worthy that the least impressive salvage rate (74 per cent) was in the group of threatened aborters who had had no previous abortions. A possible explanation for this is that these patients were less alarmed about their symptoms and therefore less prompt in reporting to their obstetricians and starting upon stilbestrol therapy.

*Stilbestrol for Abortion: Prophylactically on the Basis of Past History.*—(Table II.) Forty-one patients were treated because they had been sterile for two to ten years previously. Six of these aborted, and there was an additional fetal loss from premature delivery. Although the incidence of abortion is said to be somewhat increased in pregnancy following a period of infertility, there is no general agreement as to the validity of this statement. We cannot evaluate the results in these patients, but include them for what they may be worth. The same may be said for the group of 16 patients who were treated for surgical reasons, including fibroid uterus, previous operations on ovaries, uterus, or cervix, or operations during early pregnancy. Of the 272 women treated prophylactically, 215 were given stilbestrol because of a history of previous abortions. One hundred thirty-five had had two or more previous abortions, with an average of 2.8 per patient. One hundred five of these, 78 per cent, carried to twenty-eight weeks, and 72 per cent obtained living children. These figures compare favorably with those reported by Vaux and Rakoff in 24 women whose previous pregnancies averaged 2.9 abortions per patient and who were treated with estrogen and progesterone.<sup>17</sup> If the Smith and Smith concept is correct, stilbestrol administration should give better results than could be acquired by substitution therapy with progesterone alone or with estrogen plus progesterone (provided the cells which secrete the hormones are capable of responding to stimulation), since secreted hormones would be supplied at a more physiologic level and a more uniform rate than could be accomplished by parenteral administration.

TABLE II. STILBESTROL FOR ABORTION PROPHYLACTICALLY (ON BASIS OF PAST HISTORY)  
272 CASES\*

INDICATION FOR THERAPY	NO. OF CASES	CARRIED TO 28 WEEKS (PER CENT)	LIVING AND WELL BABIES (PER CENT)
Infertility (2 to 10 yrs.)	41	86	82
Surgical reasons	16	81	75
Previous abortions			
1	80	87	83
2	65	82	77
3	41	87	80
4 or more	29	67	52
Total	272	83	78

\*Including 9 cases on too low dosage, 3 of whom aborted, and 13 cases on too high dosage, 7 of whom aborted.

*Abortion Sequences.*—(Table III.) Of the 434 patients treated either definitively or prophylactically for abortion, 127 had had two to five consecutive abortions prior to the pregnancy in which stilbestrol was administered. Malpas,<sup>18</sup> on the basis of the known incidence of abortion in the British Empire and of the accidental and recurrent factors involved, has calculated that a woman who has aborted two recurrent gestations has a 62 per cent chance of carrying the following pregnancy, whereas if she has aborted three successive previous pregnancies her chance of carrying a fourth is reduced to 27 per cent. Eastman,<sup>19</sup> applying the same mode of calculation to the statistical analysis of abortions by American authors, arrived at approximately the same figure for those with a history of two previous abortions. His spontaneous cure rate



after three, however, is only 16.4 per cent, and if the same calculations are carried to four and five successive abortions, the spontaneous cure rate becomes 2 and 0.5 per cent, respectively. The results reported in Table III, therefore, cannot possibly be ascribed to chance, and seem to establish beyond any reasonable doubt the value of stilbestrol therapy in habitual abortion. It is to be remembered that only 15 per cent of these patients had threatened to abort when therapy was started, and comparison of the figures in Tables I and II indicates, as would be expected, that prophylactic treatment gives better results. Furthermore, many of these chronic aborters were given small doses of stilbestrol during the cycle of conception, as recommended by Smith,<sup>20</sup> for the purpose of stimulating better luteal secretion and thereby providing a more normal maternal environment from the very start. It is theoretically possible that a certain percentage of pathologic ova were averted by this means. In many of these patients the previous abortuses had been found defective.

TABLE III. STILBESTROL FOR CHRONIC ABORTION; REPEATED CONSECUTIVE ABORTIONS PRECEDING THERAPY; NO SUPPLEMENTARY THERAPY—127 CASES\*

PREVIOUS ABORTIONS	NO. OF CASES	CARRIED TO 28 WK. (PER CENT)		LIVING AND WELL BABIES (PER CENT)	
2	67	56	84	54	81
3	38	33	87	33	87
4	17	11	65	10	59
5	5	2	40	1	20
Total	127	102	80	98	77

\*Also included in Tables I and II. One hundred had no living children. Twenty-four were treated for threatened abortion; the rest prophylactically. Many (? exact number) took stilbestrol (0.1 to 0.3 mg. daily) during cycle of conception.

*Effects of Variation in the Dosage Schedule.*—Of the 18 women (Tables I and II) whose dosage of stilbestrol was considerably below that recommended, only 50 per cent carried. Of the 28 women who were given what we would consider an overdosage only 17, or 61 per cent, carried. Both of these figures are significantly below that for the group as a whole (i.e., 80 per cent of the 491 patients treated for abortion). We have considered the dosage too high if 10 mg. or more are given daily for more than 10 consecutive days before the sixth week, 25 mg. or more daily before the tenth week, 50 mg. or more before the fifteenth week, and 100 mg. or more before the twentieth week. Although most of the doctors, in treating abortion, followed the Smith and Smith schedule fairly closely up to the twentieth week, many of them felt that the full dosage was not necessary once the danger period had been passed. The effect of these variations upon later pregnancy are summarized in Table IV. All of the 99 women listed in column 2 continued to take stilbestrol through the thirty-fifth week, but the weekly increase was discontinued late in the second trimester, and in some instances the dosage was decreased by 5 mg. at weekly intervals after the twenty-fifth week, so that the final dose during the thirty-fifth week was 25 mg. instead of 125 mg. daily. These patients did as well during the third trimester as did the patients on the full Smith and Smith schedule (column 1) except for a somewhat higher incidence of late pregnancy toxemia. The incidence of premature delivery was more than doubled when stilbestrol was entirely discontinued at twenty-five to thirty-four weeks (column 3), although the fetal loss was still only 5 per cent. When it was stopped at twenty to twenty-five weeks (column 4) there was an even more marked increase in the incidence of premature delivery, a 12 per cent fetal loss due to prematurity and a considerable increase in the incidence of late pregnancy toxemia. We very much doubt if the premature deliveries in these cases were directly



due to estrogen withdrawal since the interruption of pregnancy by this means has been tried at various stages of gestation without effect. It seems more likely that many of these patients who were primarily treated for abortion had an inherent deficiency in their ability to secrete the steroid hormones which still prevailed after their usual danger period had passed and that they required the extra stimulation supplied by stilbestrol in order to carry normally to term. In Fig. 1 are presented our findings on the pregnanediol excretion of one of these patients in whom we investigated the effect of reducing the dosage of stilbestrol after her usual danger period had passed. The results indicate that in this particular patient stilbestrol in adequate amounts throughout was essential for the continued increase in pregnanediol excretion that characterizes normal pregnancy.

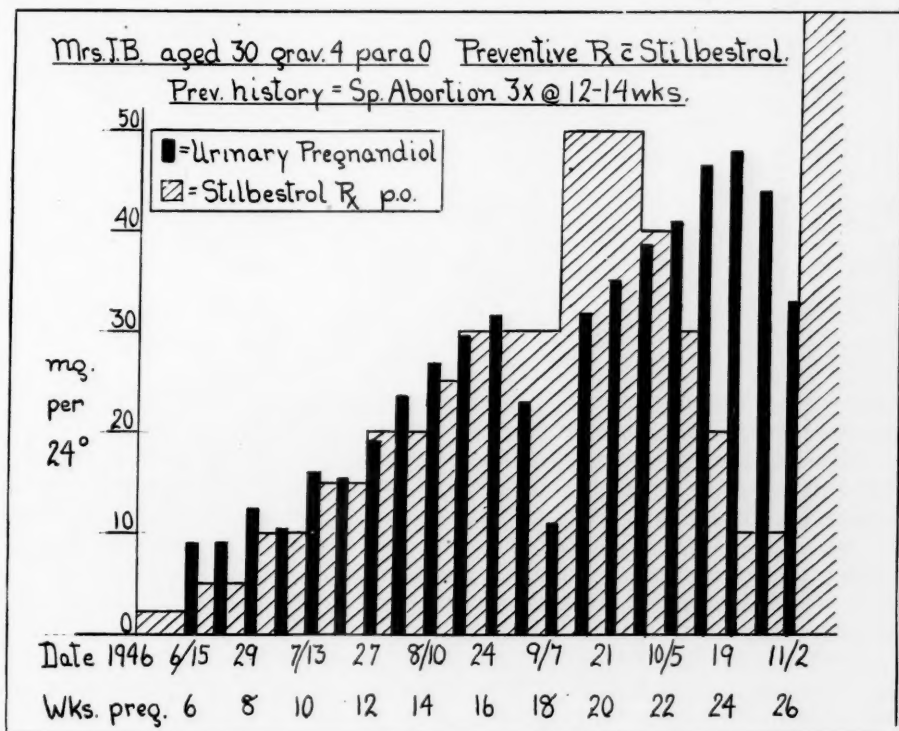


Fig. 1.—Effect upon pregnanediol excretion of two attempts to give less than the prescribed amount of stilbestrol after the patient's usual danger period had passed.

During the sixteenth and seventeenth weeks the dosage was maintained at 30 mg. instead of the usual increase of 5 mg. daily at weekly intervals. Starting at twenty-one weeks the dosage was decreased by 10 mg. daily at weekly intervals in place of the usual increase. At twenty-six weeks the dosage was increased to 75 mg. daily where it was maintained through the thirty-sixth week. She went into labor spontaneously two days after the cessation of therapy. A healthy baby (6 lbs. 2 oz.) was delivered by cesarean section and survived.

We have been concerned about the theoretical dangers of stilbestrol over-dosage. It is well known that estrogens in unphysiologic amounts are toxic to the fetuses of rodents. It has long been known, also, that the prolonged administration of large amounts of estrogen depresses the gonadotropic activity of the pituitary. Similarly, it seems likely that the continued administration of unphysiologic doses of stilbestrol during pregnancy might inhibit the placental secretion of steroid hormones and even do permanent damage to the secretory

activity of this organ. No cases in this series were given significantly larger dosages during later pregnancy than those recommended by us, but 28 patients received what we consider overdosage prior to the twentieth week. Seventeen carried to the twenty-eighth week (Table IV, column 6). Despite the continued administration of stilbestrol, over one-half of them developed later pregnancy complications with the loss of three of the 17 babies. This is a small group but the fetal loss is significantly greater than when the amounts recommended were given and the results are sufficiently alarming to convince us of the real danger of overdosage, especially during the early weeks when the placenta is assuming ovarian function in the matter of hormone production.\*

TABLE IV. STILBESTROL FOR ABORTION; EFFECT OF DOSAGE UPON LATER PREGNANCY OF 491 PATIENTS TREATED DEFINITELY OR PROPHYLACTICALLY.  
393 (80 PER CENT) CARRIED TO 28 WEEKS

DOSAGE { WEEKS	(1) S & S 7-36	(2) < S & S AFTER 20	(3) STOPPED @ 25-34	(4) STOPPED @ 20-25	(5) TOO LOW THROUGH- OUT	(6) TOO HIGH 4-20
No. of cases	213	99	19	34	9	17
Premature > 3 wks.						
Baby lived	8.8%	7.1%	21.0%	18.0%	22.0%	30.0%
Baby died	4.5%	4.0%	5.2%	12.0%	11.0%	12.0%
Toxemia						
Baby lived	1.8%	3.0%	0	8.8%	0	6.0%
Baby died	0	1.0%	0	0	0	6.0%
Total fetal loss	4.5%	5.0%	5.0%	12.0%	11.0%	18.0%
Total complications	15%	15%	26%	39%	33%	54%

*Stilbestrol Prophylactically Against Complications of Late Pregnancy.*—

In presenting the data concerning 95 patients who were given stilbestrol because of a history of late pregnancy complications, we have first summarized the total results comparing the outcome of the treated pregnancies of the group with the past obstetrical histories of these same patients (Table V). Since only 18 of their 197 previous pregnancies had been normal throughout, there were 179 abnormal pregnancies in their past histories or an average of 1.9 per patient. With such a low average incidence of previous trouble the significance of the apparent reduction, in this pregnancy on stilbestrol, in loss of the fetus from abortion, prematurity, stillbirth, and pre-eclampsia might be questioned. In the lower part of Table V, however, we have grouped these patients according to the number of previous complications that constituted the indication for stilbestrol administration. All of the complications listed are associated, we have reason to believe, with a deficiency of progesterone. If a patient has three or more pregnancies in each of which one or another of these abnormalities recurs, an inherent inadequacy may well be involved and the expectancy of a normal outcome in any succeeding pregnancy greatly reduced. In these patients a comparison of their past histories with the outcome of this pregnancy on stilbestrol would seem to be valid. There were 22 such patients. Eighty-three, or 92 per cent, of their previous 91 pregnancies were complicated by one or another of the abnormal conditions listed, and only 31, or 35 per cent, resulted in living infants. On stilbestrol these 22 patients had an incidence of 64 per cent pregnancy complications and 16, or 73 per cent, obtained living

\*Davis and Fugo<sup>21</sup> administered 50 to 200 mg. of stilbestrol daily for six to eight weeks to fifteen women between the fourth and sixteenth weeks of pregnancy, and observed no increase in pregnanediol excretion. Their published data actually reveals a decrease in urinary pregnanediol after eight to nineteen days of these very large doses. This is particularly significant, since pregnanediol excretion normally increases quite rapidly at this time. All but eight of their cases had therapeutic abortions. One of these eight had a miscarriage during the second trimester. No details were given as to the course or outcome of the other pregnancies.

children. The difference between these figures is strikingly significant. These results, although not conclusive, indicate that stilbestrol therapy for such patients may be expected to increase their chances for a normal pregnancy and a living child.

TABLE V. STILBESTROL PROPHYLACTICALLY FOR COMPLICATIONS OF LATE PREGNANCY (ON BASIS OF PAST OBSTETRIC HISTORY), 95 CASES

	PAST HISTORY		ON STILBESTROL	
No of pregnancies	197		95	
Abortions (< 22 wks.)	20	10%	3	3%
Premature (< 37 wks.)	84	43%	31	33%
died of prematurity	60	30%	11	12%
Stillborn (? cause)	28	14%	4	4%
Pre-eclampsia	47	24%	12	13%
Pre-eclampsia, baby died	22	11%	3	3%
No complications	18	9%	45	47%
Total living babies	67	34%	71	75%

Of the 95 cases on stilbestrol:

INDICATION FOR R	PAST OBSTETRIC HISTORY			THIS PREGNANCY ON STILBESTROL		
	TOTAL PREG-NANCIES	ABNORMAL	BABIES L & W	TOTAL PREG-NANCIES	ABNORMAL	BABIES L & W
1	54	87%	37%	47	53%	75%
2	52	100%	30%	26	42%	77%
3 or more	91	92%	35%	22	64%	73%

*Stilbestrol Prophylactically for Premature Delivery.*—(Table VI.) Forty-six of the patients prophylactically treated for late pregnancy complications were given stilbestrol in the hope of combating their tendency towards premature delivery. The recurrent nature of this abnormality is well recognized. Of their 93 previous pregnancies, there had been none that were carried beyond the thirty-sixth week, nine having aborted and 66 having been lost because of prematurity, making a total of only 18 living babies, or 19 per cent. About 40 per cent of them carried to term on stilbestrol. Although this is a considerable improvement over their previous histories of no term deliveries, the fact that the percentage of term deliveries on stilbestrol was uniform, regardless of the number of previous premature deliveries, suggests that in more than one-half of these cases, factors other than hormonal are predominantly involved. The fetal salvage, however, was more than tripled, even among the 12 patients who had had three or more previous early deliveries. This was in part due to the fact that most of them carried longer than in previous pregnancies, but not entirely. Several of the obstetricians noted that the placentas from stilbestrol treated patients were grossly more healthy looking and the babies unusually rugged for their gestational age. It would appear, therefore, that stilbestrol administration to these patients who repeatedly deliver early not only reduces the incidence of premature delivery, but considerably increases their chances of obtaining a living child. Our explanation would be that although the progressive deficiency of steroid hormones which invariably, according to our findings, precedes labor whether at term or prematurely, may, in most of these cases, be an end result of some more primary condition, it is still a contributory factor. By combating it the onset of labor may be postponed, but perhaps of even more importance is an increased vascularity from a higher level of estrogen and progesterone secretion, thereby providing a better maternal environment for the fetus so that when delivery does occur it is in better condition than it would have been if stilbestrol had not been given.

TABLE VI. STILBESTROL PROPHYLACTICALLY FOR PREMATURE DELIVERY; 46 PATIENTS\* WHOSE PAST HISTORIES CONTAIN NO DELIVERIES LATER THAN 36 WEEKS. NO SUPPLEMENTARY THERAPY.

PAST OBSTETRICAL HISTORIES						THIS PREGNANCY ON STILBESTROL						
PREVIOUS PREM. DELIV- ERIES	TOTAL PREG- NAN- CIES	ABORTED	PREMATURE		TOTAL L & W %	NO. OF CASES	TERM DELIVERIES		PREMATURE			TOTAL L & W %
			NO.	L & W %					NO.	BABIES		
										L & W	%	
1	19	0	19	10	10	19	9	47	10	6	60	79
2	30	1	29	31	29	15	5	33	10	5	50	67
3	21	5	16	0	0	7	3	43	4	1	25	57
4 or more	23	3	20	35	30	5	2	40	3	1	33	60
Totals	93	9	84	21	19	46	19	41	27	13	48	67

\*Also included in Table V.

*Stilbestrol Prophylactically to Pregnant Women With Known Essential Hypertension.*—(Table VII.) It is well known that essential hypertension is a predisposing factor to superimposed late pregnancy toxemia and to premature delivery. Cosgrove<sup>22</sup> has placed the fetal loss in all pregnant women with essential hypertension, regardless of severity, as high as 38 per cent. In Table VII are presented the data concerning 17 women who had been under medical care for essential hypertension before they became pregnant. Since hypertension is a progressive disease, any improvement in the outcome of this pregnancy on stilbestrol over their past obstetric histories should be highly significant. This is particularly true, since three of these women taking stilbestrol had the added hazard of carrying twin pregnancies, whereas there had been no twins in the past pregnancies of any of the seventeen cases. There were no primiparas among them, and all had had previous obstetric abnormalities. Of their 45 previous pregnancies only 6, or 13 per cent, had been uncomplicated, and the fetal loss had been 20, or 42 per cent. In this pregnancy on stilbestrol the incidence of uncomplicated pregnancies was nearly tripled, and the fetal loss was only 2, or 12 per cent. The difference between these figures is of unquestionable significance. Actually the fetal loss was only 10 per cent, since 18 out of a possible 20 infants survived. One patient separated her placenta at twenty-four weeks. The other fetal loss was in a severe hypertensive patient (blood pressure 210/110) who had albumin from the start of pregnancy and underwent cesarean section at thirty-one weeks, the infant dying of prematurity. If this patient and another with known nephritis are omitted from the series, the incidence of albuminuria on stilbestrol is only 20 per cent. If a rise in blood pressure during the last two months constitutes a diagnosis of superimposed toxemia in these patients, then seven, or 41 per cent, of the seventeen pregnancies treated had this complication. The difference between this figure and the 69 per cent incidence of increased blood pressure in their previous pregnancies is statistically significant. The only patients of this series who had any supplementary therapy were two who were on a rice diet. Both had superimposed toxemia and cesarean section before term, one of them being the patient mentioned above whose baby died of prematurity. None of the other pregnancies was artificially interrupted.

Although this is a small series of cases, the results seem sufficiently encouraging to warrant further trials of this therapy in dealing with hypertension complicating pregnancy. There is no known reason to suppose that stilbestrol could influence the disease itself or control the hypertension beyond the possibility of keeping it within the nonpregnant range, but it may well postpone the onset and reduce the severity of obstetric complications and thereby increase the fetal salvage by combating the progressive deficiency of estrogen and proges-



terone, which we believe in these cases results from vascular deficiency and which is, according to our findings, a contributory factor in all of these accidents of later pregnancy.

TABLE VII. STILBESTROL PROPHYLACTICALLY TO PREGNANT WOMEN WITH KNOWN ESSENTIAL HYPERTENSION; 17 CASES\*

	AVERAGE AGE = 33 YEARS		RANGE = 22-42 YEARS	
	PAST HISTORY		ON STILBESTROL	
No. of pregnancies	45		17	
Abortions < 22 wks.	10	22%	0	
Premature < 37 wks.	17	38%	5	29%
Stillborn (? cause)	2	4.5%	0	
Superimposed toxemia				
Rise in B.P. during last 2 months	31	69%	7	41%
Albuminuria during last 2 months	22	49%	5†	29%
No complications	6	13%	8	47%
Total fetal loss	20	42%	2	12%

\*Including three twin pregnancies; ∴ 18 of 20 babies lived. Two of the 17 were on rice diet. Both had rise in blood pressure and albuminuria. One of these babies died.

†Including two who had albuminuria throughout pregnancy (one a known nephritic).

*Stilbestrol Prophylactically to Pregnant Women with Diabetes.*—Although much of our investigative work on the complications of late pregnancy has been done in diabetic women, only nine of the present series had this disease. Two other patients whose pregnancies were complicated by diabetes and who were treated with stilbestrol were reported by us,<sup>11, 12</sup> making a total of only eleven cases to date. The diabetes of all was classified as severe. Three patients were primiparous. (These are not included in Table V.) The other eight were patients who had all had obstetrical complications in previous pregnancies. Twelve of the thirteen previous pregnancies since the onset of diabetes had been complicated by toxemia, intrauterine death or premature delivery. Only two of these thirteen pregnancies had resulted in living children. There were three fetal deaths in this series of 11 patients treated with stilbestrol but only one of these, due to spontaneous delivery at twenty-six weeks, could be considered a failure so far as stilbestrol therapy is concerned. Another was due to placenta previa, and the third was that of the baby of an Rh-negative patient who was induced at thirty-seven weeks because of a rising anti Rh titer. She had a prolonged labor, and a Braxton-Hicks delivery was performed, the infant being hydrocephalic. (There has been only one other congenital anomaly in this whole series of patients given stilbestrol, an infant with webbed fingers.) There was no toxemia in these 11 diabetic women, although 6 of them were allowed to carry to term. Three babies were described as unusually large and edematous. All three did well but their occurrence in uncomplicated pregnancies substantiates our early observation that there seems to be no connection between the large infants of diabetic mothers and the hormonal imbalance which so consistently accompanies toxemia, premature delivery and intrauterine death in both diabetic and nondiabetic women.<sup>23</sup>

Eleven cases are too few to warrant any conclusions concerning the value of stilbestrol as a preventive measure in pregnancy complicated by diabetes. It seems reasonable to assume, however, that the results would be as good as when it is used prophylactically for the same complications in nondiabetic women, since the same premature deficiency of estrogen and progesterone prevails. We are hoping that our dosage schedule will be given a more extensive trial in diabetic clinics. It is certainly a less expensive form of treatment and should be more successful than the attempt at replacement therapy with estrogen and progesterone originally proposed by us<sup>2, 24</sup> and favorably reported upon by White.<sup>25</sup>

*The Use of Stilbestrol for the Definitive Treatment of Late Pregnancy Complications.*—We have shown that stilbestrol administration alone as a definitive measure in late pregnancy toxemia is fruitless,<sup>12</sup> and we have not recommended its use in any complication of late pregnancy except as preventive therapy. Our reason for this has been the conviction that the onset of clinical signs in later pregnancy reflects a premature senility of the placenta which has already progressed to a degree that cannot be influenced by hormone administration alone. Twenty-four patients of this series, however, were so treated. Two of them, who were started on stilbestrol late in the second trimester because of the development of toxic signs, showed progressive toxemia during stilbestrol administration. The pregnancy had to be interrupted at twenty-six weeks in one of them, and the other had a stillbirth at thirty-two weeks. Twelve other patients were given stilbestrol for bleeding between weeks twenty-three and thirty-two. Three of these carried to term, but in one the only symptom was slight spotting for one day only, and the amount of stilbestrol given was too little conceivably to have influenced placental secretion. Three had premature babies that survived. One of these had a viable infant when bleeding began, and delivered spontaneously after only three days of stilbestrol administration. The pregnancy of each of the other six bleeding patients of this group terminated in spontaneous premature delivery with death of the infant.

Ten other patients were given stilbestrol because of uterine contractions with no show between weeks twenty-one and twenty-nine. Although eight of these carried to term and nine of them obtained living children, we cannot conclude that the administered stilbestrol was responsible, first, because so many patients normally carry to term after such episodes and, second, because half of these cases were given stilbestrol in such low dosages that it seems improbable that it could have had any effect.

It is, of course, conceivable that abnormal bleeding in later pregnancy might in some cases be due to local placental site pathology rather than to generalized placental senility of syncytial trophoblastic origin with its concomitant irreversible deficiency of sex steroids. In such cases stilbestrol administration might help and may have contributed to four of the six successful outcomes in the twelve patients of this series treated definitively for bleeding after the twenty-second week. It could certainly do no harm, but it seems likely that the usual obstetric measures and bed rest would be just as effective.

*Toxic Manifestations From Stilbestrol.*—In the 632 case reports that we have received to date, toxic reactions have been recorded nine times, an incidence of 1.4 per cent. Six of these patients complained of nausea, one of headaches and somnolence, one of vaginal discharge, and one of a skin rash. Four of them discontinued therapy, three with relief of symptoms and one without. The other five continued on the regular schedule and their symptoms disappeared. Whether or not such symptoms are due to the stilbestrol, it is probably only the rare case that will not be able to tolerate the full dosage schedule throughout with only temporary discomfort. For such a patient the amounts recommended may actually constitute overdosage, and the dosage given should be regulated just below the amount that brings on symptoms. A few patients, in whom therapy had been discontinued after their danger periods had passed, voluntarily began taking stilbestrol again because they claimed that they felt so much better when taking it.

### Summary

The basis for the use of stilbestrol in pregnancy is briefly reviewed, together with the indications and the dosage schedule recommended. Complete

case reports on 632 pregnant women, to whom diethylstilbestrol was given largely for the indications and in the amounts recommended by us, have been analyzed. They have been divided according to the indications for therapy, i.e., threatened abortion (219 cases), abortion prophylaxis (272 cases) and prophylaxis against late pregnancy toxemia, intrauterine death, and premature delivery (98 cases). Although we have not recommended stilbestrol as a definitive measure in later pregnancy, 24 patients were so treated and are considered separately. Nineteen cases that fell into none of these categories are omitted.

Seventy-eight per cent of the patients who were treated for bleeding between the sixth and twenty-first weeks carried to twenty-eight weeks, and 72 per cent had living and well babies. The highest spontaneous cure rate reported in the literature is 50 per cent. Eighty-three per cent of the patients who were given stilbestrol prophylactically against abortion carried to twenty-eight weeks, and 78 per cent had living and well babies. In the 127 cases who had had two to five consecutive abortions prior to the one in which stilbestrol was given, the fetal salvage averaged 77 per cent. In each group it was very significantly higher than the spontaneous cure rate as established by Malpas and Eastman. In the total 491 cases treated for abortion the incidence of abortion and of later pregnancy complications was higher when the dosage schedule was not followed than it was in the group as a whole.

In many of the patients treated prophylactically for late pregnancy complications it was impossible to evaluate the effect of stilbestrol therapy, and this part of our report must be considered preliminary. Twenty-two of them, however, had had three or more previous obstetric abnormalities, 27 had had two or more premature deliveries, 17 had known essential hypertension with bad obstetric histories, and nine had diabetes, six of these with bad obstetric histories. Considering the past obstetric histories of these patients, the course and outcome on stilbestrol gave good indication that the administration of this drug as a preventive measure may be expected to reduce the incidence of those complications of later pregnancy associated with a premature deficiency of the placental steroid hormones, estrogen and progesterone. There was even stronger evidence that the onset of these complications would be postponed and the fetal mortality reduced. The results of the use of stilbestrol as a definitive measure in later pregnancy were not promising.

### References

1. Smith, G. V., and Smith, O. W.: *New England J. Med.* 215: 908, 1936.
2. Smith, G. V., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 36: 769, 1938.
3. Smith, G. V., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 38: 618, 1939.
4. Heckel, G. P., and Allen, W. M.: *Endocrinology* 24: 137, 1939.
5. Smith, O. W., Smith, G. V., and Schiller, S.: *J. Clin. Endocrinol.* 1: 461, 1941.
6. Smith, O. W., Smith, G. V., and Schiller, S.: *AM. J. OBST. & GYNEC.* 45: 15, 1943.
7. Smith, O. W.: *Endocrinology* 35: 146, 1944.
8. Smith, O. W., Smith, G. V., and Hurwitz, D.: *Am. J. M. Sc.* 208: 25, 1944.
9. Smith, O. W., and Smith, G. V.: *Proc. Soc. Exper. Biol. & Med.* 57: 198, 1944.
10. Pencharz, R. I.: *Science* 91: 554, 1940.
11. Smith, O. W., Smith, G. V., and Hurwitz, D.: *AM. J. OBST. & GYNEC.* 51: 411, 1946.
12. Smith, O. W., and Smith, G. V.: *West. J. Surg.* 55: 288 and 313, 1947.
13. Corner, G., and Allen, W.: *Am. J. Physiol.* 88: 340, 1929.
14. Smith, G. V., and Smith, O. W.: *Physiol. Rev.* 28: 1, 1948.

15. Heuser, C. H., Rock, J., and Hertig, A. T.: Carnegie Institution of Washington Publication 557: 85, 1945.
16. Hertig, A. T., and Livingstone, R. G.: New England J. Med. 230: 797, 1944.
17. Vaux, N. W., and Rakoff, A. E.: AM. J. OBST. & GYNEC. 50: 354, 1945.
18. Malpas, P.: J. Obst. & Gynaec. Brit. Emp. 45: 932, 1938.
19. Eastman, N. J.: Habitual Abortion, Progress in Gynecology, edited by J. V. Meigs and S. H. Sturgis: New York, 1946, Grune and Stratton, Inc., pp. 262-268.
20. Smith, G. V.: New England J. Med. 230: 339, 1946.
21. Davis, M. E., and Fugo, N. W.: Proc. Soc. Exper. Biol. & Med. 65: 283, 1947.
22. Cosgrove, S. A.: The Clinical Management of Toxemias of Pregnancy. Presented at the Conference on Normal and Pathological Physiology of Pregnancy, sponsored by the Committee on Human Reproduction of the National Research Council in behalf of the National Committee on Maternal Health, January 31, 1948.
23. Smith, O. W., and Smith, G. V.: AM. J. OBST. & GYNEC. 33: 365, 1937.
24. Smith, G. V., and Smith, O. W.: AM. J. OBST. & GYNEC. 39: 405, 1940.
25. White, P.: J. A. M. A. 128: 181, 1945.



## RENAL RESPONSE TO THERMAL STIMULUS\*†

L. D. ODELL, M.D., G. T. ARAGON, M.D., AND R. C. SMITTER, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital)

APPARENTLY several kinds of environmental stimuli will cause an elevation of blood pressure. Among these are exposure to cold or irritant gases, pain, situations disturbing the emotions, breath holding, muscular activity, and sudden changes in gravity. Extreme degrees of lability following such stimuli have been interpreted as evidence of a prehypertensive state.<sup>1</sup> Thus, various "tests" have been devised, principally to standardize the stimulus employed.

The most commonly used method for determining vascular lability employs exposure to cold. Ordinarily the subject's hand is plunged into ice water to the wrist for one minute, blood pressure changes being recorded before, during, and following this experience.<sup>1</sup>

It is reasonable to suppose that any such experience violently affecting blood pressure might also alter other body functions. Chesley et al<sup>2</sup> reported an increased proteinuria immediately following the "cold test." Dieckmann and Michel<sup>3</sup> noted various untoward symptoms and signs following immersion; these included persistent hypertension, blurred vision, epigastric pain, hematuria, and two instances of vascular collapse. Paroxysmal cold hemoglobinuria is found sporadically, and Tottermann<sup>4</sup> observed two instances in which convulsions were precipitated by cold exposure. Ariel et al<sup>5</sup> found anuria in rabbits subjected to temperatures of 3° C. for periods up to forty-eight hours. Garai,<sup>6</sup> using the standard cold test, noted an increased response in shipwrecked sailors, these men having been previously exposed to immersion in arctic waters. And Horvath et al<sup>7</sup> studied Army volunteers under conditions of extreme cold and found a progressive increase in basal metabolic rate.‡

It has been noted previously that the urine volume per minute and urea clearance rate are suppressed following a prolonged cold test.<sup>8</sup> The present study reports findings following a fifteen-minute immersion of one hand, or foot, in an ice-water bath at a temperature of 1° C. An increased secretion of posterior pituitary substances is suggested as a contributory cause for this phenomenon.

### Materials and Methods

A total of 66 patients were used. These included 22 with toxemia of pregnancy, 33 during normal pregnancy, one with diabetes insipidus and pregnancy, one with a glioma of the spinal cord and pregnancy, and nine who were not pregnant. Two of the latter had hypertension or a history of previous toxemia of pregnancy.

\*Presented before the Chicago Gynecological Society, Nov. 21, 1947.

†This study was supported in part by the Chicago Lying-in Hospital Fiftieth Anniversary Fund for Research on Eclampsia and Puerperal Fever.

‡For an additional review of this subject see Dieckmann and Michel,<sup>3</sup> Chesley et al,<sup>2</sup> and Garai.<sup>6</sup>

Following an eight-hour fast, intravenous fluids, consisting of 5 per cent glucose in distilled water, were administered at a constant rate (6 to 8 ml. per min.) from 6 A.M. until completion of the test. Urine specimens were collected by catheter each half hour until three specimens of approximately equal amount were obtained. The third specimen served as the control period (Cl-1). The patient's hand or foot was then immersed to the wrist (or ankle) in an ice water bath maintained at a temperature of 1° C. for a fifteen-minute period; and urine specimens were collected after completion of this immersion (Cl-2), after the succeeding fifteen minutes (Cl-3), and upon completion of a final one-half hour collection (Cl-4). Blood pressure, pulse, respirations, and fetal heart rate were obtained at regular intervals. Urine chlorides and urine proteins were estimated by the usual methods. Urine specific gravity was obtained gravimetrically using 2 ml. pyknometer bottles, a suitable correction being made for the protein content.

### Results

1. *Rate of Urine Flow.*—Data are divided into two groups: (1) Cases having no significant change, or even an increase in minute volume as a result of ice immersion; and (2), those having a diminished urine excretion (Figs. 1 and 2). In this latter group, following a control period (Cl-1), the minute volume dropped sharply during ice immersion (Cl-2), although the antidiuretic effect was often more pronounced during the succeeding fifteen minutes (Cl-3). The rate of flow during Cl-4 tended to return to that of Cl-1. Three-fourths of the patients subjected to the test had this suppression. The mean and maximum rise in systolic and diastolic blood pressure was slightly more in those showing a decreased excretion than in those without. The reaction was non-specific in that pregnancy toxemia occurred in both groups. In general, patients experiencing great discomfort from immersion had a urine suppression. A fifteen-minute episode of anuria occurred in one pre-eclamptic case (Figs. 3 and 4).

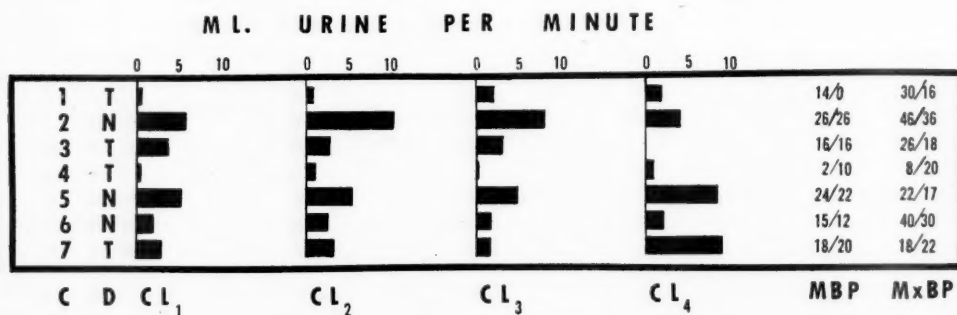


Fig. 1.—Renal response to thermal stimulus. Cases without urine suppression. C = Case number. D = Diagnosis: T — Toxemia of pregnancy, N — Normal pregnancy; Cl-1 to 4 = Consecutive clearance periods; MBP = Mean blood pressure change, mm. Hg; MxBP = Maximum blood pressure change, mm. Hg. Immersion in ice water bath during second (Cl-2) clearance period.

2. *Proteinuria.*—Findings are plotted graphically (Fig. 5). These illustrate a slight trend toward an increased excretion per minute of protein during and following ice immersion. But comparison of numbers in Fig. 5 with Figs. 1 and 2 discloses that degrees of change in blood pressure do not necessarily correlate with the amounts of protein excreted. It is difficult to reconcile such findings with those of Chesley et al.,<sup>2</sup> who noted a direct relationship between an increase in proteinuria and the degree of rise in blood pressure, and who ob-

served that this proteinuria followed the release of "vasospasm" attending the increased pressure. In some patients in this series the amount of protein excreted/minute actually remained the same or became reduced.

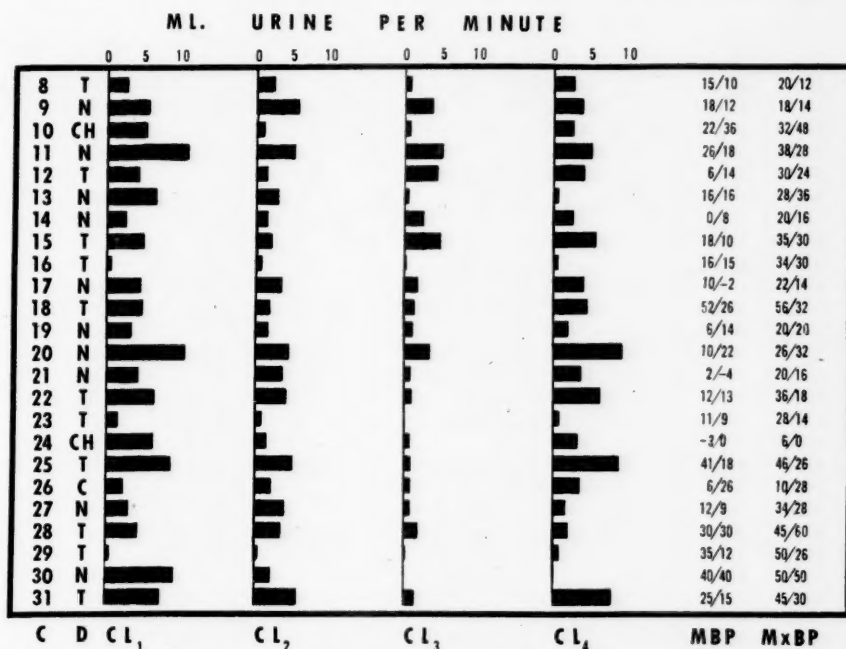


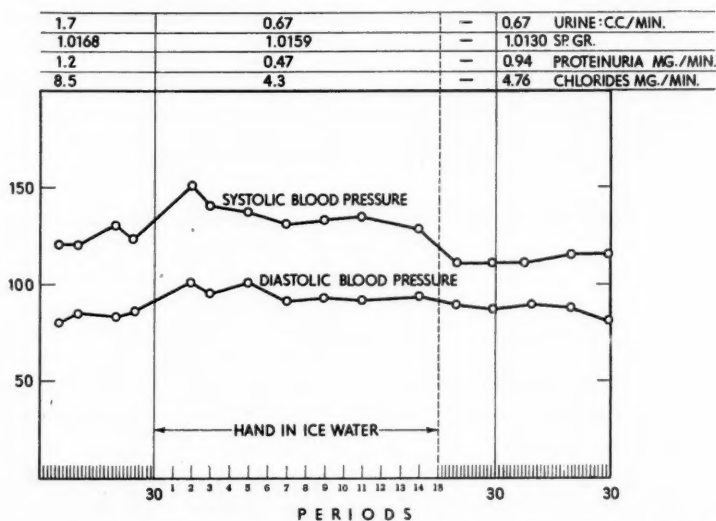
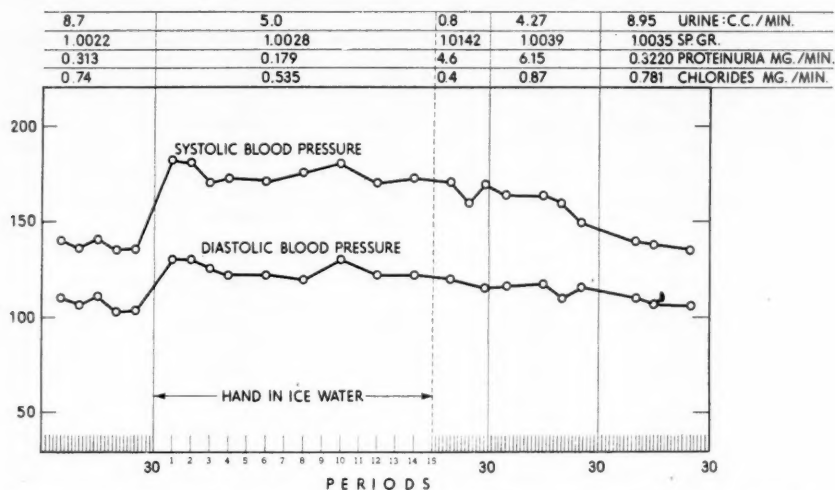
Fig. 2.—Renal response to thermal stimulus. Cases with urine suppression. C = Case number; D = Diagnosis: T - Toxemia of pregnancy, N - Normal pregnancy, CH - Non-pregnant with hypertension, C - Nonpregnant without hypertension; CL-1 to 4 = Consecutive clearance periods; MBP = Mean blood pressure change, mm. Hg; MxBP = Maximum blood pressure change, mm. Hg. Immersion in ice-water bath during second (CL-2) clearance period.

3. *Specific Gravity and Chloride Excretion.*—In most instances, as the urine volume lessened during CL-3, the specific gravity and concentration of chlorides increased (Fig. 6). This is reasonable since specific gravity depends, in part, upon the chloride content of the urine. Reasons for change in the output of chlorides are problematical. The amount of this salt excreted by the kidneys largely depends upon certain extrarenal factors, its plasma concentration, and the rate of its reabsorption, presumably in the distal convoluted tubules;<sup>9</sup> and this latter factor bears directly to the filtration rate and/or the activity of the posterior pituitary gland.

4. *Blood Pressure, Pulse, Respiration, Fetal Heart Rate, Subjective Symptoms, and Microscopic Examinations of the Urine.*—In most instances the initial sharp rise in blood pressure during immersion was not sustained, but tended to fall gradually as the pain sensation, elicited by the cold, subsided. Although this time interval was variable, it usually lasted four to five minutes in duration. In some patients the blood pressure was even less following cold immersion than previous to it.

In this series all the patients experienced cold and some degree of pain. The latter, usually deep and throbbing, was finally replaced by a sensation of pins and needles, and this was followed by a complete numb adaptation to the stimulus. Several subjects complained of a sharp, cramping epigastric pain which tended to disappear within a few minutes. One (See case 28, Fig. 2)

experienced anginal-like symptoms during immersion. The blood pressure in this case rose from 230/130 to 290/195 mm. Hg. Although the hand was kept immersed for only two minutes out of a fifteen-minute clearance period, a marked suppression occurred in the rate of urine excreted.



A slight decrease in pulse and respiratory rate occurred during immersion. The mean fetal heart rate did not vary significantly. Examination of the urine of several subjects disclosed no significant change in cellular constituents per unit of time following the test.

5. *Effect of Anesthesia.*—Patients were tested by immersion of one hand, or one foot, in ice water during ethylene, cyclopropane, or spinal anesthesia. There was no significant rise in blood pressure in these cases. This agrees with Wolff and Hardy<sup>10</sup> who observed that the rise in blood pressure was due to the



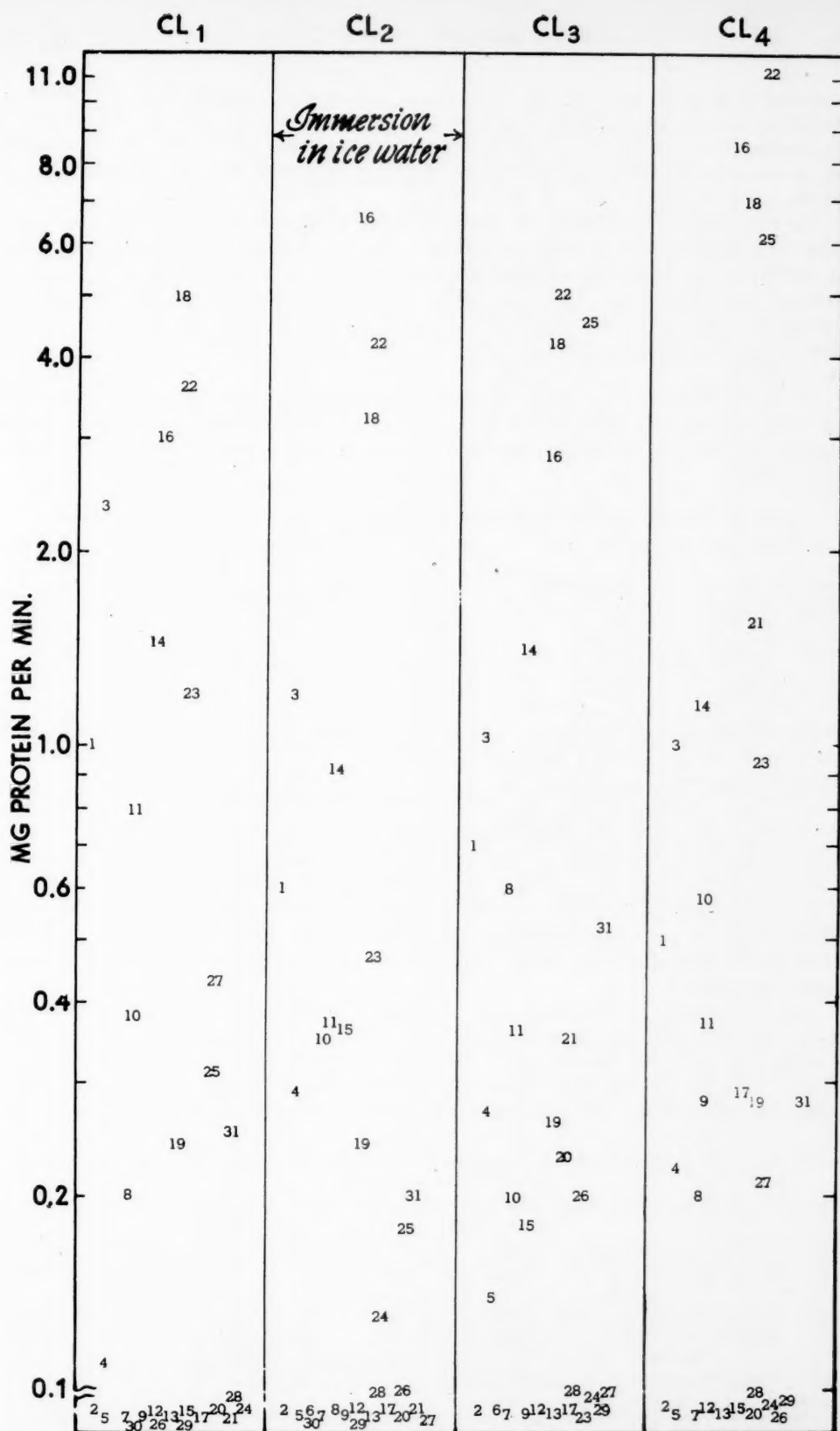


Fig. 5.—Renal response to thermal stimulus. Effect of ice immersion on protein excretion. Protein excretion expressed as mg. protein per minute on semi-log scale. CL-1 to 4 = consecutive clearance periods.

conscious cold pain elicited by immersion. However, anesthesia, particularly inhalation anesthesia, which obliterates consciousness, may not prevent a urine suppression from immersion. This might become initiated at the site of immersion or as a result of a nerve-conducted reflex to lower centers of the nervous system.

To test this hypothesis four patients were observed under inhalation anesthesia and three under spinal anesthesia. Identical conditions concerning fasting, intravenous fluids, and constant urine excretion were obtained. The foot was used for immersion. Three patients were observed prior to this test without anesthesia, and had a characteristic urine suppression as a result of cold. Inhalation anesthesia was maintained at a stage deep enough to abolish any sensation of pain.

Table I shows the results of patients observed under gas anesthesia. In each case there was a decrease in urine excretion during and following ice immersion. In two instances the blood pressure fell slightly, and in the other two it rose.

TABLE I. EFFECT OF ICE IMMERSION ON URINE EXCRETION DURING ANESTHESIA

IDENTIFICATION	ANESTHETIC	ML./MIN.				MBP
		CL-1	CL-2	CL-3	CL-4	
K. B. 158861	None	2.6	1.7	2.5	2.7	0/8
	Ethylene	0.27	0	0.53	0.47	-20/-15
S. S. 319945	None	6.7	3.0	0.54	0.6	20/22
	Ethylene	1.8	1.7	0.6	1.7	-5/2
F. W. 394087	None	3.4	1.7	1.2	2.0	8/12
	Ethylene	1.46	0.4	0	0.29	12/20
P. H. 386325	Cyclopropane	8	0.71			50/30

MBP = Mean change in blood pressure.

Immersion in ice-water bath during CL-2

Three patients tested under spinal anesthesia by immersion of one foot in an ice-water bath had no significant change in urine excretion per minute.

Such evidence would indicate that a reflex path exists which is independent of conscious pain but which is abolished by spinal anesthesia, and therefore not initiated locally by some hormonal secretion at the site of immersion. It does not, however, explain whether it is entirely sensory or whether it is of a sensory-endocrine pattern.

The following three cases seem to illustrate this last possibility. The first was a patient with far-advanced cervical carcinoma upon whom a cordotomy, severing the spinal-thalamic tract, had been performed at thoracic 3, above the source of renal innervation. The second case was a patient, near term, with a glioma at cervical 4. Anesthesia of the lower extremities was present in both

TABLE II. EFFECT OF ICE IMMERSION ON URINE EXCRETION IN PRESENCE OF CORD INTERRUPTION

IDENTIFICATION	DIAGNOSIS	EXTREMITY USED	ML./MIN.				MBP
			CL-1	CL-2	CL-3	CL-4	
M. K. 250289	Spinal cord tumor—C4	Foot	4.5	6.0	4.6	4.6	0/6
M. D. 352809	Cordotomy—T-3	Foot	5.0	4.3	4.9		10/0
J. F. 389835	High spinal anesthes.—T-5	Hand	1.1	1.2	0.2	0.8	10/16

MBP = Mean change in blood pressure.

Immersion in ice-water bath during CL-2

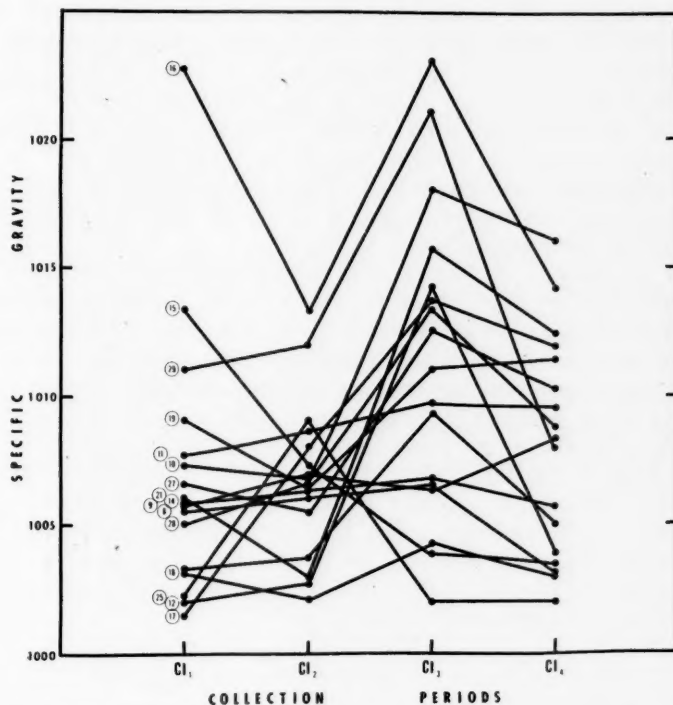


Fig. 6.—Renal response to thermal stimulus. Effect of ice immersion on urine specific gravity. Cl-1 to 4 = Consecutive clearance periods. Immersion during Cl-2.

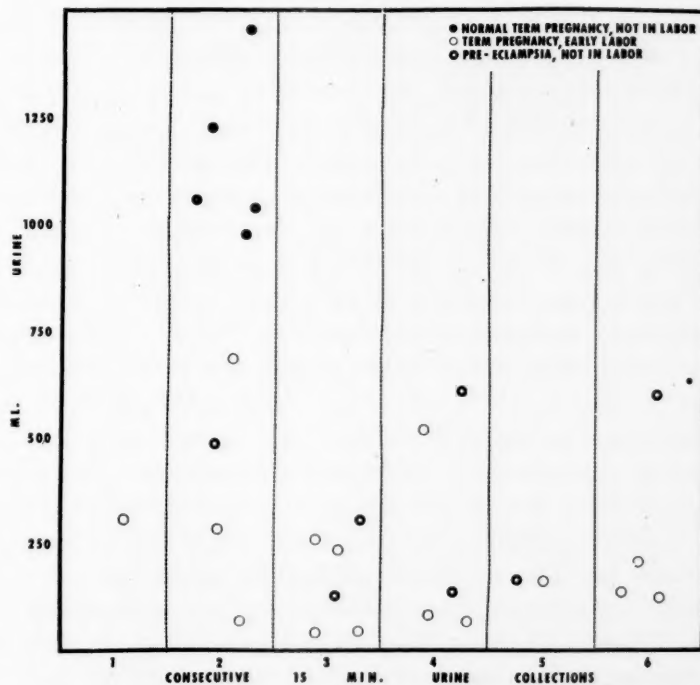


Fig. 7.—Renal response to thermal stimulus. Response to intravenous fluids. 1,000 ml. 5 per cent glucose commenced intravenously fifteen minutes previous to first urine collection and completed within twenty minutes.

instances. In neither did immersion of one foot for fifteen minutes in an ice-water bath result in a decreased urine excretion. A third patient, however, in labor, was given a high spinal anesthesia to the level of thoracic 6. And immersion of one hand resulted in a reduced urine excretion (Table II).

Therefore, evidence obtained under anesthesia would suggest a sensory-humoral sequence, present during inhalation anesthesia, not secreted locally at the site of immersion, independent of the blood pressure response; probably stimulating a subcortical center, possibly the hypothalamus and pituitary gland, the latter liberating an antidiuretic hormone.

6. *Effect of Labor.*—It seems reasonable that the decrease in urine flow occurring during labor may be due in part to pain and apprehension. Verney<sup>11</sup> demonstrated a lag between absorption and excretion of lavaged water in dogs, a phenomenon attributed to the antidiuretic action of the posterior pituitary gland, which must be overcome before diuresis occurs. Employing this principle, patients were given 1,000 ml. 5 per cent glucose intravenously over a twenty-minute period before labor, and during early labor without sedation. The results (Fig. 7) indicate that the maximum diuresis occurs within thirty minutes in the former group, and the total urine flow usually exceeds 1,000 ml. within one and one-half hours. In the second group, however, the period of maximum diuresis is often delayed, and the total urine flow is much less for a comparable period. The same test on seven pre-eclamptic patients not in labor showed a similar anti-diuresis.

### Comment

According to accepted theories, changes in the volume excretion of urine depend upon either the filtration rate or rate of tubular reabsorption, or both. Among the several factors influencing the former are: variations in filtration surface and changes in intracapsular pressure, renal blood flow or plasma protein content; while tubular reabsorption depends upon the rate of urine flow through tubules as well as upon the antidiuretic effect of the posterior pituitary gland. Either mechanism would explain a suppressed excretion following ice immersion. Wolf<sup>12</sup> obtained variable figures for renal blood flow and glomerular filtration (using diodrast and inulin methods) following cold exposure, but observed a sharp depression of both functions and a depressed urine excretion after other painful stimuli. Verney,<sup>11</sup> however, using a thermostromuhr on the denervated dog kidney, recorded only a transient fall in renal blood flow following an electrical stimulus to subcutaneous tissues. This same investigator attributed the antidiuresis after such stimulus to a posterior pituitary effect. Recently, Trueta et al.<sup>13</sup> report that renal arterial blood can be diverted past the kidney cortex to the medulla by sciatic nerve stimulation in dogs. Roentgenograms of the kidneys, following intra-arterial injection of radio opaque material, confirm this shunt, since there is a nonvisualization of the ipsilateral renal cortex, while the contralateral organ and the medulla of the ipsilateral side can be easily outlined. Urine excretion from the stimulated kidney is reduced. Apparently, some subcortical plexuses of vessels acts as the shunting route. Which of these three mechanisms might explain the urine suppression following ice immersion is largely problematical.

During normal pregnancy the kidney rarely concentrates chlorides well, the average being 0.5 Gm. per cent.<sup>14</sup> During toxemic pregnancy this value



is even lower, 0.185 Gm. per cent in 26 eclamptics. In patients with oliguria following eclampsia or abruptio placenta, we often observe a low urine specific gravity. Although these specimens appear to be concentrated, and contain considerable protein, the chloride content and corrected specific gravities are often low.

The fact that urine excretion was suppressed in some cases (Table II) without an appreciable rise in blood pressure, and the observation that the maximum reduction in urine flow occurred following (instead of during) changes in blood pressure, causes one to speculate that the two phenomena may be coincidental. Wolff and Hardy<sup>10</sup> showed that the hypertension following ice immersion is a measure of the subject's reaction to cold pain. They also detected a local vasospasm during the experience and noted an increased cold pain if vasoconstrictor drugs, i.e., solution of posterior pituitary or epinephrine, were administered during immersion. It was, however, concluded that ischemia from spasm did not cause the pain.

Lipschitz and Stokey<sup>15</sup> have observed that the mechanism of antidiuresis is not a single one. They postulate (1) an acetylcholine-antidiuretic hormone mechanism, arising from stimulation of the posterior pituitary gland, (2) one associated with renal innervation, being absent in animals with denervated kidneys subjected to injections of morphine, and (3) a humoral factor different from the antidiuretic hormone. Of these, the first, that involving the posterior pituitary gland, would seem to explain the antidiuretic effect of ice immersion.

On the other hand, it is difficult to explain the antidiuresis following ice immersion as being entirely due to a posterior pituitary stimulation since a decreased renal blood flow and glomerular filtration rate have been observed following painful stimuli,<sup>12</sup> and even following exposure to the cold test.<sup>16</sup>

Smith,<sup>17</sup> in a recent review, traces the neural pathways controlling the pituitary gland. The mammallion hypophysis consists of neural and glandular portions. The posterior lobe comprises the neural portion and the pars intermedia of the glandular portion. It is in the pars nervosa that the antidiuretic hormone is elaborated. And this tissue receives nerve fibers from several hypothalamic nuclei, but chiefly from the bilateral supraoptic nuclei. These tracts become destroyed in diabetes insipidus. It is of interest that one patient in this experiment had diabetes insipidus, yet exhibited a suppression of urine flow following ice immersion.

Brun et al.<sup>18</sup> studied kidney function during the transient circulatory collapse produced by a prolonged upright position on a tilt table, and found the inulin and diodrast clearances reduced during and following this experience. It was concluded that the reduced urine flow from the collapse was due to an increased secretion of an antidiuretic hormone. Drury et al.<sup>19</sup> made similar observations following the continuous pressure breathing of oxygen. Bradley and Bradley<sup>20</sup> found kidney function suppressed during increased intra-abdominal pressure. It would seem that the same mechanism was responsible for the decreased urine flow following syncope, pressure breathing, and increased intra-abdominal pressure; and possibly following immersion in ice water.

### Summary

The immersion of one hand, or foot, in an ice-water bath maintained at a temperature of 1° C. results in a decreased urine flow.

This phenomenon is associated with an increase in the specific gravity of urine, and in some instances, a change in protein excretion per minute.

Variations in systolic and diastolic blood pressure accompany this experience but do not correlate, in the degree of the response, with the protein excretion per minute.

The fetal heart rate does not vary significantly. Maternal pulse and respiratory rates tend to decrease.

Experiments to date conducted under anesthesia indicate that ice immersion may stimulate the liberation of an antidiuretic hormone. The site of liberation is probably not within the immersed limb, or within the kidney. Evidence presented supports its origin as being above the level of cervical 4. The phenomenon is apparently not abolished by inhalation anesthesia. It is believed that the site of liberation may be the posterior pituitary gland.

The authors are indebted to Dr. Wm. J. Dieckmann for advice concerning this study.

### References

1. Hines, E. A., Jr., and Brown, G. E.: *Proc. Staff. Meet., Mayo Clin.* 10: 371, 1935.
2. Chesley, L. C., Markowitz, I., and Wetchler, B. B.: *J. Clin. Investigation* 18: 51, 1939.
3. Dieckmann, W. J., and Michel, H. L.: *Arch. Int. Med.* 55: 420, 1935.
4. Tottermann, L. E.: *Acta med. Scandinav.* 124: 446, 1946.
5. Ariel, J., Bishop, F. W., and Warren, S. L.: *Cancer Research* 3: 449, 1943.
6. Garai, O.: *Brit. Heart J.* 7: 200, 1945.
7. Horvath, S. M., Golden, H., and Woger, J.: *J. Clin. Investigation* 25: 709, 1946.
8. Odell, L. D., and Aragon, G.: *AM. J. OBST. & GYNEC.* 54: 867, 1947.
9. Farnsworth, E. B.: *Am. J. Med.* 1: 246, 1946.
10. Wolff, S., and Hardy, J. D.: *J. Clin. Investigation* 20: 521, 1941.
11. Verney, E. B.: *Lancet* 251: 739, 1946.
12. Wolf, G. A.: *Research Publ., J. Nerv. & Men. Dis.* 23: 358, 1943.
13. Trueta, J., Barclay, A. E., Daniel, P., Franklin, K. J., and Prichard, M. M. L.: *Lancet* 251: 237, 1946.
14. Dieckmann, W. J.: *AM. J. OBST. & GYNEC.* 29: 3, 1935.
15. Lipschitz, W. L., and Stokey, E.: *Am. J. Physiol.* 148: 259, 1947.
16. Talso, P. J., Crosley, A. P., and Clark, R. W.: *J. Lab. & Clin. Med.* 33: 430-434, 1948.
17. Smith, H. W.: *Bull. New York Acad. Med.* 23: 177, 1947.
18. Brun, C., Knudsen, E. O. E., and Raaschou, F.: *J. Clin. Investigation* 25: 568, 1946.
19. Drury, D. R., Henry, J. P., and Goodman, J.: *J. Clin. Investigation* 26: 915, 1947.
20. Bradley, S. E., and Bradley, G. P.: *J. Clin. Investigation* 26: 1010, 1947.

5841 MARYLAND AVENUE

### Discussion

DR. ARTHUR K. KOFF.—The secretion of urine by the normal kidney is dependent on a number of variable factors. (1) The renal blood flow, which is dependent on blood pressure, and the calibre (diameters) of the afferent and efferent arterioles of the glomerulus. A narrowing (constriction) of the afferent arteriole results in a decreased blood flow to the glomerular tufts, which in turn results in decreased secretion of urine. (2) The amount of urine secreted through the glomerular capsule depends on the filtration pressure which is determined by the difference between intraglomerular pressure, the resistance of the capsular membrane and the oncotic or osmotic pressure, particularly the blood proteins. It is estimated that 180 liters of urine are secreted through the glomerular capsule daily. Of this amount 177 liters of water and threshold substances are reabsorbed by the proximal and distal convoluted tubules and particularly in the loop of Henle. Chlorides are said to be absorbed in

the distal convoluted tubule. The antidiuretic hormone is responsible for 20 per cent of the water reabsorbed. The lack of this hormone is responsible for the marked diuresis in diabetes insipidus, and conversely an increase in the antidiuretic hormone could cause a more rapid reabsorption of urine from the tubules resulting in a marked decrease in urine output.

Dr. Odell has shown that under the influence of a standard pain stimulus (immersion of the hand in cold water) there is an initial rise in blood pressure due to generalized vasospasm. Apparently spasm of the arterioles to the glomeruli produces a decreased renal blood flow, and consequent decrease in urine excretion. However, the blood pressure returns to normal in five to eight minutes, but the decrease in urine output during the following fifteen minutes is even greater than the previous period of the test. This phenomenon he suggests may be due to the stimulation of the neuro hypophysis through the hypothalamus, and the release of antidiuretic hormone. The increase in this hormone causes increased reabsorption of water by the kidney tubules, and a consequent decrease in excretion of urine.

Dr. Odell's contention is supported by the work of Dieckmann and Michel who showed similar urinary excretion curves after the injection of posterior pituitary extract.

Verney, in 1946, by injecting hypertonic salt solution into the carotid artery of dogs, showed a similar urinary excretion curve which was abolished by hypophysectomy. Moreover, his experiments suggest that the blood chlorides to a great extent control the release of antidiuretic hormone by the posterior pituitary.

It is possible, therefore, that the oliguria and occasional anuria recognized in severe pregnancy toxemias may be due to the effect of the antidiuretic hormone rather than to the vascular spasm associated with the increased blood pressure.

As a matter of fact Putnam and Teel, many years ago, demonstrated antidiuretic substances in the urine of pregnant women with severe toxemia.

DR. WM. J. DIECKMANN.—This report by Dr. Odell forms part of the study he is making on blood pressure and renal function.

The obstetrician sees more cases of oliguria and anuria than almost any other specialist, with the exception of the urologist. This work demonstrating the close connection in some patients between external stimuli and urine output indicates the possibility of a combination of conditions under which the pregnant patient can be placed that might result in oliguria. A decrease in the urine output is found in eclampsia, in certain patients with hypertension, with hypotension from shock, and also in cases with peritonitis. A simple deprivation of water within a couple of hours in a very hot, dry atmosphere, may result in anuria.

The work also demonstrates that the kidney is not an isolated organ. Ten years ago we talked about "kidney disease," "liver disease," etc., but now we know that these various organs do not act as units but are dependent upon each other and the condition of the body as a whole.

DR. ODELL (Closing).—Our interest in this problem relates to studies on the oliguria and anuria in patients with toxemia of pregnancy. One should recognize that the kidney will respond to various sorts of external and internal stimuli by a reduction in urine flow. Although such changes may not be of importance to the normal individual, they may become irreversible in the pathologic state, particularly in those conditions in which the vascular system is already disturbed.

The relief of pain in toxemic patients becomes a real problem. The usual drugs employed (such as morphine and sodium Amytal) pharmacologically have an antidiuretic effect. We have administered sodium Amytal intravenously to toxemic patients and noted this antidiuretic effect is independent of changes in the glomerular filtration rate (mannitol) and renal blood flow (para-amino hippuric acid).

## ELDERLY PRIMIPARAS\*

WILLIAM F. GEITTMANN, M.D., JAMES E. FITZGERALD, M.D., AND  
BRUCE P. ZUMMO, M.D., CHICAGO, ILL.

*(From the Obstetrical Service of St. Luke's and Cook County Hospitals, Chicago, and from the Department of Obstetrics and Gynecology of Northwestern University Medical School)*

THIS is a study of elderly primiparas, 35 years of age and over, taken from the records of St. Luke's and Cook County Hospitals in Chicago, Ill. It was necessary to review a larger number of years at Cook County to collect the same number of cases as at St. Luke's. The cases from Cook County are those of a purely charity service and those from St. Luke's are predominantly private cases of a closed staff. The patients considered are all individuals who were pregnant 7 months or more and who had viable babies on admission to the hospital. The oldest primipara at St. Luke's was 48 years of age and the oldest at Cook County was 45 years of age. A study of Table I shows that the patients at Cook County were predominantly Negro, while those at St. Luke's were predominantly white. It is noted that the percentage of elderly primiparas was five times as much at St. Luke's as in the Cook County patients. The number of patients in each age group was approximately equal for both hospitals as were the types of presentation. The incidence of breech presentation in each series was almost 6 per cent, as compared to 3 per cent in patients of all ages. Usually a higher incidence of twins is noted in elderly primiparas but there was only one set in 417 cases. Shoulder presentations are also supposed to occur more frequently in elderly primiparas but there was only one in the entire group.

The maternal mortality rate for all patients at both hospitals is very much the same, as may be seen in Table II. However, the maternal mortality rate of elderly primiparas in the private patients was more than twice the general mortality rate, whereas there were no deaths in the Cook County series. We still feel that a higher mortality can be expected in these elderly primiparas, due to age and accompanying degenerative diseases and the increased frequency of cesarean section. In most of the reports on elderly primiparas, maternal deaths occurred most frequently following cesarean section. Therefore, we feel that cesarean section should be carefully considered before being done and every effort made to deliver these patients from below. The one death in this series followed as an immediate operative complication of cesarean section. The section was done on a 37-year-old primigravida after a twenty-hour labor of poor quality with indifferent contractions, 9 cm. dilatation, ruptured membranes of three and one-half hours' duration, and the head not impressible below the spines. A normal male child was delivered. The uterus failed to contract under massage, Ergotrate and Pituitrin, and it continued to remain flabby and a considerable amount of bleeding ensued. A hysterectomy was decided upon because of the impossibility of controlling bleeding. As the clamps

\*Presented before the Chicago Gynecological Society, Oct. 17, 1947.



were being applied to the broad ligament, the patient ceased to breathe. Resuscitation by stimulants and artificial respiration were useless. Autopsy revealed acute pulmonary atelectasis.

TABLE I

ST. LUKE'S, JAN. 1, 1939, TO JULY 1, 1947		TOTAL	PER CENT
All cases delivered, 7 months and over		10,447	
Elderly primiparas delivered, 7 months and over		214	2.05
Primiparas, aged 35 to 39 inclusive		181	84.6
White	152		
Negro	29		
Primiparas aged 40 and over		33	15.4
White	28		
Negro	5		
Vertex presentations		202	94.4
Breech presentations		12	5.6
COOK COUNTY, JAN. 1, 1937, TO JULY 1, 1947		TOTAL	PER CENT
All cases delivered, 7 months and over		50,677	
Elderly primiparas delivered, 7 months and over		203	0.4
Primiparas aged 35 to 39 inclusive		172	84.7
White	54		
Negro	118		
Primiparas aged 40 and over		31	15.3
White	11		
Negro	20		
Vertex presentations		189	93.1
Breech presentations		12	5.9
Transverse presentation		1	0.5
Multiple pregnancy		1	0.5

TABLE II. MATERNAL MORTALITY

St. Luke's total cases	10,447	
St. Luke's total case deaths	21 or 0.2	per cent
Cook County total cases	50,677	
Cook County total case deaths	80 or 0.15	per cent
St. Luke's elderly primiparas	214	
St. Luke's elderly primiparas deaths	1 or 0.46	per cent
Cook County elderly primiparas	203	
Cook County elderly primiparas deaths	0 or 0.0	per cent

The fetal mortality rate was corrected to exclude all deaths except those due to an obstetric cause. Those babies dead on admission were excluded. Table III shows that the fetal mortality rates of all cases at St. Luke's and Cook County ran closely parallel, with a slightly higher rate in the Cook County series. This might be explained by the fact that many of these patients had no prenatal care. Along with this neglect of prenatal care, there was a higher incidence at Cook County of pre-eclampsia with its accompanying higher fetal mortality. The fetal mortality in the elderly primiparous series at Cook County was much

TABLE III. FETAL MORTALITY (CORRECTED)

	TOTAL	DEATHS	PER CENT
<i>All Cases.—</i>			
Cook County	50,677	1,035	2.04
St. Luke's	10,447	140	1.3
<i>Elderly Primiparas.—</i>			
Cook County	203	8	3.94
St. Luke's	214	2	0.93

higher than in the private series. This may be explained by the higher rate of cesarean section at St. Luke's, the slightly lower incidence of toxemia and syphilis, and the fact that all patients had adequate prenatal care. In reviewing the fetal deaths in this series, it would seem that severe pre-eclampsia caused quite an increase at Cook County. A résumé of the fetal deaths follows:

### St. Luke's Hospital

1. A severe pre-eclamptic at term entered the hospital in false labor. Patient was treated conservatively and blood pressure dropped. Six days after admission, patient went into labor spontaneously and after twelve hours of labor the fetal heart tones disappeared. Twenty-four hours later she delivered a 3-pound stillborn infant.

2. Patient febrile on admission to the hospital, fetal heart tones 180, patient in poor or questionable labor. Vaginal examination early in labor revealed wide separation of sutures of baby's head and it was questionable as to whether this was a baby in good condition. Vaginal delivery was decided on. After 128 hours of labor, baby was delivered by midforceps after Dührssen's incisions. Baby died in twelve hours and autopsy revealed tentorial tear.

### Cook County Hospital

1. Pre-eclamptic of eight months' gestation, with blood pressure of 170/95 and 3+ albumin. Patient was treated conservatively for twelve days and went into spontaneous labor. Heart tones were lost after four hours of an eight and one-half hour labor. Autopsy revealed subaponeurotic hematoma.

2. Pre-eclamptic at term who had had no prenatal care. Entered the hospital in labor with blood pressure 190/120 and a 3+ albumin. Heart tones disappeared just before patient delivered after a nine hour labor. Autopsy revealed a congenital atelectasis, intrameningeal hemorrhages, and hemorrhage into the orbits.

3. Thirty-nine-year-old mild pre-eclamptic one month from term with partial abruptio. Baby delivered after a three hour labor, gasped a few times and could not be revived.

4. Seven months' gestation in a 39-year-old woman under treatment for syphilis. After a four and one-half hour labor, a 2-pound, 2-ounce baby delivered by breech. Baby died in twenty-four hours.

5. Forty-year-old pre-eclamptic of seven months' gestation with a blood pressure of 165/110, 2+ albumin, and thrombophlebitis. After a twenty-nine hour labor, patient spontaneously delivered a 3-pound baby who lived three hours. Autopsy revealed massive intraventricular hemorrhage of the brain.

6. Forty-year-old pre-eclamptic of eight months' gestation with a blood pressure of 180/126, 2+ albumin, and in labor with ruptured membranes. Baby delivered by breech after fifteen and one-half hours' labor and died four days alter. Autopsy revealed atelectasis and petechial hemorrhages of pleura, pericardium, and peritoneum.

7. Thirty-eight-year-old pre-eclamptic with blood pressure 168/92, 2+ albumin, and in labor. After twenty-one hours of labor, head was delivered by low forceps but shoulders were caught by constriction ring. This relaxed after thirty minutes and baby was delivered dead.

8. Thirty-eight-year-old diabetic with temperature of 102° F. entered ward and immediately delivered baby by breech. Baby died after several hours and autopsy revealed intracranial hemorrhage.

The more common complications of pregnancy as well as labor are shown in Table IV. With the increase in the age of the patient, there is an increase in the degenerative diseases, particularly of the cardiovascular and nephritic systems. There was a high incidence of pre-eclampsia and hypertensive toxemia. Fibroids were also a common complication in these older women. Prolonged labor was one of the most common complications. There was a much higher incidence of postpartum hemorrhage in the private series, but we feel this is due to the increase in the percentage of operative deliveries, necessitating deeper anesthesia. The high incidence of abruptio is expected to run parallel to an

increase in the number of toxemia cases. It was of unusual interest that in two cases of pulmonary embolism complicating the puerperium, both followed a myomectomy done at cesarean section.

TABLE IV. COMMON COMPLICATIONS OF PREGNANCY, LABOR, AND PUERPERIUM  
IN ELDERLY PRIMIPARAS

COMPLICATIONS	ST. LUKE'S	COOK COUNTY
Pre-eclampsia	23	27
Fibroids	10	11
Hypertensive toxemia	4	15
Syphilis	1	15
Pyelonephritis	2	1
Diabetes	1	2
Abdominal pregnancy	0	1
Prolonged labor	50	26
Postpartum hemorrhage	12	2
Abruptio placentae	5	4
Placenta previa	0	6
Pulmonary emboli	2	0

Table V shows the various types of vaginal deliveries. There were one-half as many spontaneous deliveries on the private service, twice as many low forceps, and twenty-one times as many midforceps. There were twice as many prolonged labors in the private series, which may explain the higher incidence of forceps deliveries. We think it is important again to emphasize the low incidence of postpartum hemorrhage in the Cook County series where the vaginal operative procedures were held down to a minimum. The high operative incidence had no marked effect on the fetal mortality in the private series where a low percentage of 0.9 per cent was obtained.

TABLE V. VAGINAL DELIVERIES

TYPE	ST. LUKE'S	COOK COUNTY
Spontaneous	55	113
Low forceps	83	42
Midforceps	21	0
Spontaneous breech	1	8
Breech with forceps to head	6	0
Breech extraction	0	2

The vaginal deliveries in these elderly primiparas were analyzed for type of labor. Short labor extended to a period of ten hours, average labor to twenty-four hours and prolonged labor to twenty-four hours and over. The shortest labors were approximately the same at both hospitals, in that they were about three hours' duration in the 35 to 39 year age group and approximately seven hours' duration in the 40 year age group. The longest labors in the 35 to 39 year age group were 128 hours at St. Luke's and 84 hours at Cook County. The longest labor in the 40 year and over age group was 42 hours at St. Luke's and 30 hours at Cook County. It can be seen from Table VI that, of the vaginal deliveries, approximately 75 per cent deliver with a short-to-average labor. Age after 35 is not too important a factor in the length of labor, as there appears to be no difference in the percentage in the various types of labor in the 35 to 39 age group and the 40 and over age group.

It is noted from Table VII that the incidence of cesarean section was 22.4 per cent in the St. Luke's series, as compared to a general average of 4.4 per cent for all patients delivered. The incidence of cesarean section at Cook County was 18.2 per cent where a general average of under 2 per cent exists. The

indications in the vast majority of cases were purely obstetric and only after an adequate trial of labor. The abdominal pregnancy delivered a living baby which is now 3 years old, healthy, and normal. Cephalopelvic disproportion and pre-eclampsia were the main reasons for low cervical cesarean sections, while fibroid uteri were the predominating cause for Porro section. It is well to remember that the only death in this series followed as an immediate operative complication of cesarean section. The high incidence of cesarean section may be justified also by the fact that these are important babies to an elderly mother and this broadens our indications. However, we feel that in view of the fact that approximately 80 per cent of these elderly patients will deliver vaginally and that almost 75 per cent of the vaginal deliveries were short or average labors, an adequate trial of labor is indicated before cesarean is resorted to.

TABLE VI. DURATION OF LABOR (EXCLUDING CESAREAN SECTION)

	ST. LUKE'S		COOK COUNTY	
	NO.	PER CENT	NO.	PER CENT
<i>35 to 39 Years of Age.—</i>				
Short	35	23.6	60	42.5
0-10 hours				
Average	72	48.6	62	42.5
10-24 hours				
Prolonged	41	27.7	19	13.4
24-hours and over				
<i>40 Years of Age and Over.—</i>				
Short	4	22.2	6	25.0
Average	9	50.0	14	58.3
Prolonged	5	27.7	4	16.6

TABLE VII. CESAREAN SECTIONS

	ST. LUKE'S	COOK COUNTY
<i>Type.—</i>		
Low cervical	37	26
Porro	11	10
Extraperitoneal	0	1
Abdominal pregnancy (living baby)	0	1
	22.4%	18.2%
<i>Indications (Low Cervical).—</i>		
Cephalopelvic disproportion	17	8
Pre-eclampsia	5	10
Breech (with or without labor)	4	0
Uterine dysfunction	3	7
Fibroids (1 obstructing birth canal)	3	0
Elective	2	0
Double uterus, twins, previous myomectomy	3	2
placenta previa, transverse presentation		
<i>Indications (Porro).—</i>		
Fibroids	9	7
Elective	1	0
Hemorrhage following low cervical	1	0
Cervical dystocia with double mitral murmur	0	1
Previous myomectomy	0	
Abruptio placentae with Couvelaire uterus	0	1

### Summary

1. This is a study of elderly primiparas, 35 years of age and over, who were of approximately seven months' gestation and who entered the hospital with viable babies.



2. Elderly primiparas occur five times more frequently in the private series than on a charity service.
3. Breech presentation occurred twice as often in elderly primiparas as in all cases.
4. Only one multiple pregnancy and one shoulder presentation occurred in 417 cases of elderly primiparas.
5. The maternal death rate was 0.46 per cent in elderly primiparas at St. Luke's as compared to 0.2 per cent in all cases; while at Cook County it was 0 per cent as compared to 0.15 per cent in all cases.
6. Corrected fetal mortality was 0.9 per cent and 3.94 per cent, respectively, at St. Luke's and Cook County hospitals, as compared to 1.3 per cent and 2.04 per cent in all cases.
7. Pre-eclampsia, hypertensive toxemia, and fibroids are the most common complications of pregnancy in elderly primiparas.
8. Prolonged labor occurred in 23.3 per cent of the elderly patients at St. Luke's and 12.8 per cent at Cook County.
9. Postpartum hemorrhage occurred more frequently in elderly primiparas at St. Luke's, where there was a higher operative incidence.
10. Approximately 80 per cent of the elderly primiparas will deliver vaginally and 75 per cent of these with short or average labors.
11. The cesarean section rate was 18.2 per cent at Cook County and 22.4 per cent at St. Luke's, as compared to 2 per cent and 4.4 per cent in all cases. Pre-eclampsia and cephalopelvic disproportion predominate as reasons for low cervical cesarean section, while fibroid uteri were the main reason for Porro section.

104 S. MICHIGAN AVENUE

### Discussion

DR. CHARLES EDWIN GALLOWAY.—It is very interesting to note that 6 per cent of the cases were breech presentation, which is almost twice the usual incidence of breech. It is also interesting, but not surprising, to find that, in a private hospital, the primiparas over the age of 35 are about five times as numerous as in a large charitable service. The men at Cook County Hospital are to be congratulated on having no maternal deaths, but the fetal deaths were four times as great per 100 cases as in the private hospital. It would make one wonder if pediatrics at Cook County Hospital would be a factor in this high fetal death rate as well as obstetrics. The statement is also included that at Cook County Hospital there is no prenatal care. Also, the incidence of cesarean section for elderly primiparas at Cook County Hospital was considerably lower than at St. Luke's. It would seem, therefore, that prenatal care, more liberal use of cesarean section, and better pediatrics at Cook County Hospital would result in lower fetal mortality among the babies of elderly primiparas.

The only maternal death among the entire series was apparently due to hemorrhage. To-day, the country over, hemorrhage has taken first place in the cause of maternal mortality. This is partly on a relative basis by having toxemia and infection reduced, but it is mainly because of our lack of adequate blood in the maternity wards and the fact that blood is not used as often and as soon as it should be.

One question which I would like to ask is: Why were the cases excluded when the patient was admitted with the baby dead in utero? The second question is: Why is there no prenatal care for patients delivering at the Cook County Hospital? Is there not something that can be done through the municipal government that might result in compulsory

care if there is such a large number who do not now receive prenatal care on the voluntary basis? The third question which I would like to present is: Should we not use cesarean section more liberally in these elderly primiparas, rather than using it less? As surgery advances, the risk becomes less each year and it would seem that a fetal death rate four times as high in Cook County with fewer cesareans would mean that it should have been used oftener. Also, section should probably have been done in the only two cases of fetal death in the series at St. Luke's Hospital, rather than delivery from below, because one was a case of severe eclamptic toxemia and the other mother was allowed to be in labor 128 hours and then had her labor terminated by Dührssen's incision and midforceps. So far, in my twenty-four years of rather active practice I have not done any Dührssen's incisions.

I think the conclusion to be reached by this paper, as stated by the authors, is that 80 per cent of elderly primiparas will deliver their babies through the birth canal and 75 per cent of those will have an average-to-short duration of labor. I also think we are justified in drawing the conclusion that, when an obstetrician assumes the responsibility for an obstetric patient who has her first baby in the later years of her reproductive life, he assumes more responsibility than if the patient were at the age of 20 to 35 which seems to be the optimal time for a woman to reproduce.

DR. J. E. FITZGERALD.—I would like to answer a question or two of Dr. Galloway. Concerning prenatal care at the Cook County Hospital, one-third of the patients have prenatal care at the hospital clinic, one-third have prenatal care in other institutions, and one-third have no prenatal care. Dr. Galloway's question is well put, what should be done about it? As far as I am concerned, he can answer it.

I do not think it was the lack of pediatric care that was responsible for the deaths of eight babies in the Cook County series. Almost all of those were premature babies born to mothers with severe toxemias. Whether or not there were any pediatricians there, the salvage rate in babies born to mothers who have severe toxemia is much lower than where the mothers have no toxemia.

I am also quite certain that doing cesarean section on mothers who have babies that are markedly premature and who, themselves, have a severe toxemia will not result in any increase of the fetal salvage. Out of the entire series, only the patient who had a cesarean section died. Probably it is not too wise to increase the incidence of cesarean section in order to save premature babies of mothers who have severe toxemia, even though they happen to be over 35 years of age.

DR. GEITTMANN (Closing).—In this study we were primarily interested in learning whether these fetal deaths were due to obstetric causes, bad delivery, bad judgment in taking care of the patients while in labor or just before they went into labor, so we excluded those patients whose babies were dead on admission.

Answering Dr. Galloway's question, the woman who was in labor 128 hours was febrile when she came in. On admission the fetal heart rate was 180. It was felt that this was not a baby in good condition and that it would be better to deliver her from below, although cesarean section was considered.

## VITAMIN B COMPLEX IN NEONATAL FEEDING

S. CHAS. KASDON, M.D., BOSTON, MASS., AND EDWARD L. CORNELL, M.D.,  
F.A.C.S., CHICAGO, ILL.

*(From the Obstetrical Department of the Henrotin Hospital)*

THE oft-quoted statement of Oliver Wendell Holmes that "a pair of substantial mammary glands have the advantage over the two hemispheres of the most learned professor's brain in the art of compounding a nutritive fluid for infants" must be considered in a new light, since the importance of vitamins in the diet of infants has been elucidated. That human breast milk as well as cow's milk is deficient in vitamins A, C, and D has long been recognized, and the use of these factors to supplement infant feeding has had wide acceptance. The part played by the vitamin B complex of factors has unfortunately been widely disregarded, in spite of accumulating evidence that it too is inadequate in most instances. Hoobler, Outhouse, and Macy<sup>1</sup> demonstrated, for instance, that whereas 2.0 c.c. of human breast milk daily were adequate in vitamin A content to prevent xerophthalmia in rats, fully 20 to 25 c.c. of human milk were essential to offer sufficient vitamin B complex for approximately normal growth, reproduction, and lactation.

The value of the vitamin B complex in infant feeding has begun to receive recognition especially in the diet of the premature infant. Barnes and Willson<sup>2</sup> have advised the use of concentrated whole yeast extract in the diet of premature infants, and this tendency has been noted in many premature nurseries. It has, however, been more or less neglected as a supplemental factor in normal term infant feedings in spite of repeated expressions in the literature advising its more extensive use. With this in mind it was felt pertinent to evaluate the effect of vitamin B complex when added to the diet of normal newborn infants in the first ten days of life on the initial weight loss, the rate of return to the birth weight, and the weight at discharge. Osborne and Mendel<sup>3</sup> demonstrated that the vitamin B requirements of rats increased rapidly with an increasing rate of growth, and it is obvious that growth in infants is most rapid in the first three months of life when the increment in weight is expressed as a per cent of the birth weight. Bloxsom<sup>4</sup> administered the mixed vitamin B to 34 young infants, as well as infants up to 2 years of age, and found that they gained an average of 100 per cent more in weight each day and remained in the hospital one-third less time. It is significant in his group of cases that a single premature received vitamin B complex from the second day of life, while the others were not placed on this supplement for two to three weeks after birth, and this premature infant gained relatively more rapidly than any of the others studied.

The mothers of all the babies here studied represent a cross-section of the population which subsist on a somewhat better than average income. Private patients made up 36 per cent of the control group and 34 per cent of the vitamin B complex group. The remaining 64 per cent of ward-service cases in the control group and 66 per cent in the vitamin B complex group came from a better than average economic population than is ordinarily seen on the ward service. From this alone it is felt that the vitamin B complex status of these parturients is certainly no worse than any comparable sample of patients in this country.

### Method

A total of 108 alternately unselected infants admitted to the neonatal nursery from the delivery room were given an aqueous extract\* containing standard vitamin B complex factors. The remaining 138 infants were used as controls. The dose of extract administered was 0.12 c.c. (2 minims) of extract to 30 c.c. (ounce) of feeding. The average intake of human or cow's milk for each infant was 300 c.c. daily with a minimum of 210 c.c. and a maximum of 420 c.c. equally distributed in both groups. Over 75 per cent of the infants accepted approximately 300 c.c. of milk daily, and the approximate quantity of measurable vitamin B factors administered to each infant daily is shown in Table I. The exact quantity of each vitamin received daily was, of course, determined by the volume of milk fed to the infant. Those infants receiving artificial formulas had the extract added directly to the milk mixture. The breast-fed infants were offered a proportionate amount of extract in between-feeding water dependent in quantity upon the difference in ante-prandial and post-prandial weight. The vitamin factors were added to the 5 per cent beta-lactose or other solution used in the first two days of life preceding the onset of regular feedings in all babies. The only difference in the management of the *control* and *vitamin B complex* series was the addition of the vitamin factors in the latter. Premature infants of less than 2,500 Gm. birth weight, those over 4,500 Gm., and those with marked abnormalities (erythroblastosis fetalis 1, mongolian idiocy 2, spina bifida 1) were excluded from the series studied since the inclusion of these infants in the relatively small number studied might seriously have altered the statistical significance of our results. The number of infants thus eliminated from the series was approximately equal for both groups (nine from control group and seven from B complex group). The birth weight curves for both series followed one another and also the normal standard curve of distribution closely with no significant variation, ranging from 2,500 Gm. (1 per cent for controls and for B complex) to a peak at 3,500 Gm. (10 per cent for both series). All weights were determined under identical conditions by but two nurses at the same hour each day. Males made up 57 per cent of the control series and 63 per cent of the B complex fed infants. The type of feedings offered in both groups is shown in Table II and reveals no significant variation in either group.

\*The quantity of the factors per c.c. of B complex administered can be found in the following table as computed by Parke-Davis and Co. and S. M. A. Co. from whom the material was obtained.

Thiamin	0.25 mg. per c.c.
Riboflavin	0.20 mg. per c.c.
Nicotinic acid	1.25 mg. per c.c.
Pyridoxine	0.10 mg. per c.c.
Pantothenic acid	0.25 mg. per c.c.
Other undetermined fractions not measured.	



TABLE I. QUANTITY OF B COMPLEX FACTORS ADMINISTERED DAILY TO MORE THAN 75 PER CENT OF ALL TEST INFANTS

Thiamin	0.30 mg.
Riboflavin	0.24 mg.
Nicotinic acid	1.50 mg.
Pyridoxine	0.12 mg.
Pantothenic acid	0.30 mg.

TABLE II. TYPE OF FEEDING. CONTROL TOTAL—138, B COMPLEX TOTAL—108

	BREAST		ARTIFICIAL		BREAST AND COMPLEMENT	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Control	34	25	18	13	86	62
B complex	22	20	18	17	68	63

### Results

From Fig. 1 it can be seen that the weight loss expressed as a per cent of the birth weight is approximately the same in both groups for three days after birth. This apparently demonstrates that there is no change in the physiological weight loss of the first three days of life which can be related to the presence of vitamin B complex in the diet. The weight gain which becomes apparent on the fourth day of life shows no significant early difference for either the control infants or those offered vitamin B complex. However, beginning on the seventh day and continuing until discharge on the tenth day of life there is a significant difference in weight gain for the two groups. The increase in weight gain for the B complex series is from 20 to 50 per cent greater than that for the control series in the last four days of the study.

The day on which the infants returned to birth weight in both control and B complex groups is shown in Fig. 2. Again it is clear that there is no significant difference between the return to birth weight of the control infants and those offered vitamin B complex until the seventh day of life. From that day to the day of discharge from the neonatal nursery the infants receiving added vitamin B complex in their diets returned to birth weight at a significantly higher rate. At discharge the cumulative difference in return to birth weight was more marked, with 80 per cent of those infants receiving vitamin B complex having returned or surpassed their birth weight, as compared to 59 per cent of the control infants who had regained their birth weight. Statistical analysis of this data for its probable significance reveals that, since all other things can be considered equal in both groups, the addition of vitamin B complex to the diet of the infants increased their chances of return to birth weight in the last four days of their stay in the neonatal nursery by 65 to 90 per cent.

When the significance of the return by 80 per cent of the B complex infants to birth weight on the tenth day of life is evaluated statistically as opposed to the control group of 59 per cent who returned to birth weight on this day, the results are very striking. The significance of these results are in the order of  $1 \text{ in } 2.4 \times 10^{18}$ , a ridiculously small chance for error.

### Discussion

The growing frenzy of vitamin therapy and prophylaxis which has swept the pharmaceutical industry and medical practice has also invaded the newborn nursery to an irregular degree. As is frequently the case, enthusiasm far outstrips clinical and laboratory knowledge in these matters. The voluminous lit-

erature and widely variant practices adhered to in many newborn nurseries prompted this definitive study of the effect of a vitamin mixture of several factors of the B complex when added to the routine neonatal feedings.

The minimum daily requirement of the B complex vitamins have never been completely established for infants, but reports of Knott<sup>5, 6</sup> suggested 0.25 mg./kg. of body weight or 0.4 mg. daily for thiamin chloride as the minimal daily requirement and this agrees well with the levels suggested by the Committee on Food and Nutrition.<sup>7</sup> The average thiamin levels reported recently for various milks are as follows: pasteurized cow's milk 0.026 mg. per 100 c.c.; boiled pasteurized cow's milk 0.024 mg. per 100 c.c.; evaporated cow's milk reconstituted with equal parts of water 0.019 mg. per 100 c.c.; human breast milk 0.020 mg. per 100 c.c. Thiamin chloride, a heat labile substance, tends to be even further depressed below the minimal daily requirements by the general practice of heating cow's milk in the preparation of infant feeding formulas. Riboflavin has also been studied in regards to the minimal daily requirements in infancy. As early as 1879 Blyth<sup>9</sup> reported the presence in cow's milk of a substance which he called "lactochrome" that is apparently identical with riboflavin. According to levels set by the Committee on Food and Nutrition<sup>7</sup> the minimal daily requirement of riboflavin for infants under one year of age is established as 0.6 milligram. The riboflavin content of human milk has been reported as 0.16 mg. to 0.52 mg. per liter, and cow's milk, 1.0 mg. to 1.5 mg. per liter by Neuweiler<sup>10</sup> who considered both sources as border line for the infant's needs. At these values an infant would require a minimum of 1,000 c.c. of breast milk daily for its riboflavin requirements. Sherman and Lanford<sup>11</sup> felt that milk is a dependable source of riboflavin for the infant, although Goodman and Gilman<sup>12</sup> state that but 20 per cent of the mother's intake of riboflavin is excreted in her milk. A possible case of ariboflavinosis in a premature infant has been reported by Stevenson.<sup>13</sup> The minimal daily requirement of nicotinic acid for infants under 1 year of age has been set at 4.0 mg. daily by the Committee on Food and Nutrition.<sup>7</sup> Standards for the other components of the B complex vitamins have not yet been adequately established for small infants.

Macy, Outhouse, Graham, and Long<sup>14</sup> found that 20 to 25 c.c. of cow's milk daily were necessary for the support of normal growth, reproduction, and lactation in rats. They felt that impaired growth of young rats during the lactation period is due essentially to the deficiency in the quantity of vitamin B complex in the mother's food supply, since three to five times the normal quantity of vitamin B complex was essential for an adequate supply of these factors in the milk.<sup>15</sup> They further stressed the fact that pooled human breast milk taken from individuals subsisting on an average American diet is deficient in vitamin B complex. Further, Cowgill<sup>16</sup> demonstrated that subclinical vitamin B complex deficiency exists widely in the United States, as did Hoobler<sup>17</sup> for infants.

Hess<sup>18</sup> stated as an incidental finding in a study of the therapeutic value of yeast and wheat embryo in infantile scurvy that a definite increase in appetite and growth was noted in the yeast fed infants. Lactating rats were found by Sure<sup>19</sup> to increase rapidly in weight when vitamin B complex was added to the

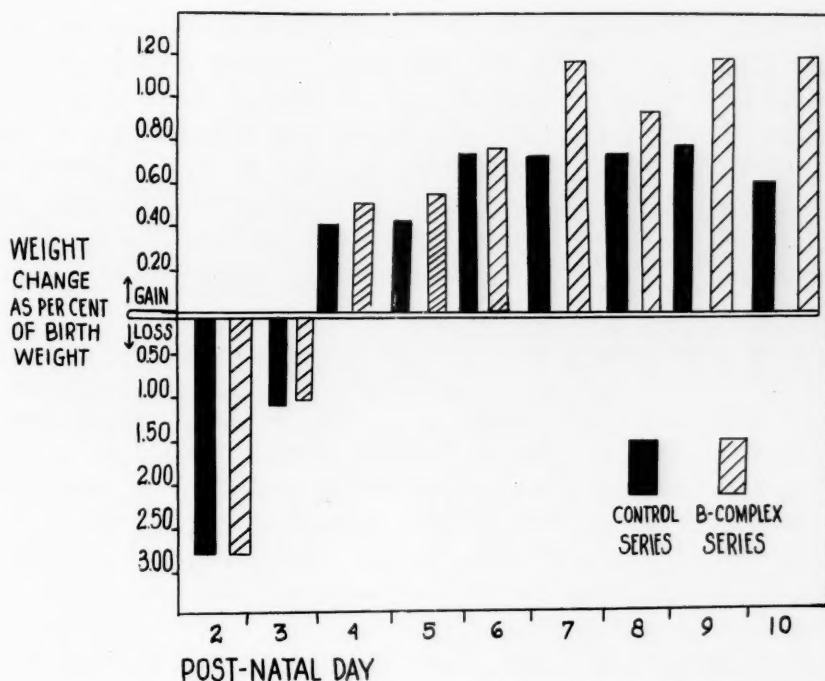


Fig. 1.—Average daily weight gain or loss as a per cent of birth weight.

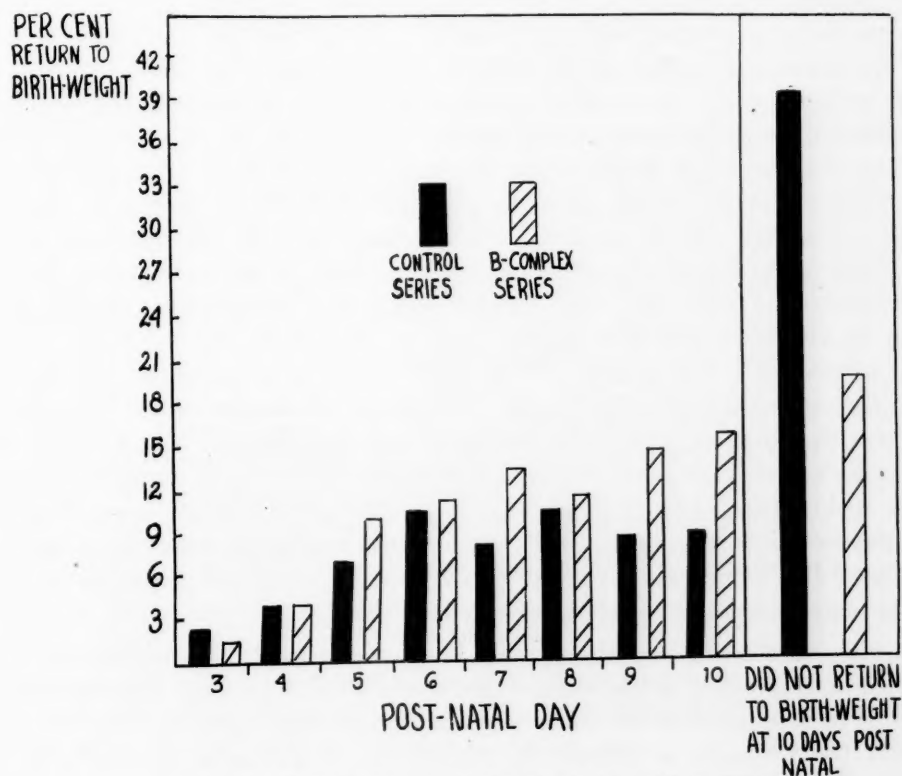


Fig. 2.—Day of return of infants' weight to birth weight.

diet. Dennett<sup>20</sup> gave 150 infants a diet rich in vitamin B complex, and found that the weight gain in five months was significantly greater than in controls without the wheat germ sugar mixture. He strongly advised the routine use of vitamin B complex in the diet of infants. Gaynor and Dennett<sup>21</sup> added rice polishings as a source of vitamin B complex in the diet of 100 normal infants which had as controls 50 infants on the same rations without rice polishings and 20 infants on a simple cow's milk formula. The weight gain of those infants on the diet supplemented by rice polishings was uniformly greater than in either of the control series.

Although Elias and Turner<sup>22</sup> reported no noticeable improvement in growth in 121 babies given brewer's yeast as a supplement to the diet over a long period of time, this evidence must be considered in the light of the excessively large quantities of brewer's yeast which are required for effective levels of B complex vitamins. Price,<sup>23</sup> on the other hand, reported that the addition of a vitamin B adsorbate to the diet of young infants resulted in a statistically significant increase in growth rate. A close relationship between vitamin B deficiency in the mother and premature labor was suggested by Clausen,<sup>24</sup> who also reported a definite augmentation of growth rate in premature infants offered supplementary vitamin B complex in their diet. Litchfield and his collaborators<sup>25</sup> and others have reported similar results.

The study here reported demonstrates sufficiently gross differences both in weight gain and in number of infants returning to birth weight within the first 10-day period of neonatal life. If there is any correlation between economic status and adequacy of diet in this country, both groups of patients can be considered as in a better than average state of nutrition. However, irrespective of the problem of variability and adequacy of the maternal diet, the fact that both groups of mothers were obtained without discrimination from identical sources suggests that there should be no significant difference in the antenatal vitamin levels of either the control or B complex groups. In order to eliminate variations which might be due to abnormal infants, those of excessive birth weight, prematures under 2,500 Gm., and infants in any way embarrassed during parturition by the usual obstetric factors were eliminated from either series at the time of admission to the nursery. This served but to clarify the premise that in the two groups of infants studied the only factor which separately identified a group was the presence or absence of the vitamin B complex. The parents, the birth weights, the method of choice of each group, the type of feeding, the sex, and the technique of handling the infants showed no significant variations. A compound containing many of the B vitamins was employed rather than specific members of this group, since the parts played in growth by the various factors in the B complex have not yet been clearly elucidated.

In view of the fact that the vitamin B complex content of both human milk and cow's milk are not considered adequate, the newborn infant may be considered to be in straitened circumstances as far as these factors are concerned. The fact that the response to vitamin B complex in weight gain is usually rapid enough to be noted in a few days suggested that a study of this effect in the first



ten days of life, that period usually spent in the obstetric nursery, was warranted. This is especially true since the weight gain is ordinarily very rapid in this period and the requirements of the infant for the essential factors present in the vitamin B complex especially great. It is felt that the material here presented demonstrates clearly that the addition of vitamin B complex to the diet of normal neonatal infants results in a significant increase in weight gain which becomes manifest at about seven days of life. This difference in weight gain is most notable when the number of infants returning to birth weight by the 10th day of life is compared in the two groups. It is therefore suggested that the diet of normal neonatal infants, as well as prematures, be supplemented by the addition of B complex vitamins to both breast-fed and artificially-fed infants from the onset of feeding.

### Summary

1. Both cow and human milk are at the border line of the minimal daily requirements for infants with respect to thiamin and riboflavin content.

2. The usual practice of heating artificial cow's milk formulas employed in the feeding of infants further depresses the thiamin content of the milk.

3. Two closely comparable groups of infants were studied, the only significant difference being the addition of vitamin B complex to one group. The group of 108 infants given vitamin B complex during the first ten days of life showed an appreciable increase in weight gain during the last four days of the study as compared with 138 control infants. In addition, whereas 59 per cent of the controls had returned to birth weight by the tenth day of life, 80 per cent of the infants administered vitamin B complex had surpassed their birth weight by this day. Statistical analysis of the results reveals a ridiculously small chance for error in interpretation of the significance of the differences in weight gain and rate of return to birth weight in both groups studied.

4. It is suggested that vitamin B complex be added to the routine feedings of neonatal infants from the onset of feeding.

We would like to express our gratitude to Alan E. Rich, Longmeadow, Mass., for his statistical analysis of the data presented.

### References

1. Hoobler, B. R., Outhouse, Julia, and Macy, Icie G.: *Tr. Am. Pediat. Soc.* **38**: 38-40, 1926.
2. Barnes, A. C., and Willson, J. R.: *J. A. M. A.* **119**: 545-547, 1942.
3. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **63**: 233-238, 1925.
4. Bloxsom, A. P.: *Am. J. Dis. Child.* **37**: 1161-1168, 1929.
5. Knott, Elizabeth M.: *J. Nutrition* **12**: 597-611, 1936.
6. Knott, Elizabeth M.: *Proc. Soc. Exper. Biol. & Med.* **45**: 765-766, 1940.
7. Recommended Dietary Allowances, Revised, 1945. Reprint and Circular Series, Number 122, August, 1945. National Research Council, 2101 Constitution Avenue, Washington, D. C.
8. Knott, Elizabeth M., Klieger, Sarah C., and Schlutz, F. W.: *J. Pediat.* **22**: 43-49, 1943.
9. Blyth, A. W.: *J. Chem. Soc.* **35**: 530-539, 1879.
10. Neuweiler, W.: *Klin. Wchnschr.* **16**: 1348-1350, 1937.
11. Sherman, H. C., and Lanford, Caroline S.: *J. A. M. A.* **110**: 1278-1280, 1938.
12. Goodman, L. S., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 1253.
13. Stevenson, S. S.: *Yale J. Biol. & Med.* **14**: 403-405, 1942.

14. Macy, Icie G., Outhouse, Julia, Graham, Alice, and Long, M. Louisa: J. Biol. Chem. 73: 189-192, 1927.
15. Evans, H. M., and Burr, G. O.: J. Biol. Chem. 76: 263-272, 1928.
16. Cowgill, G. R.: J. A. M. A. 98: 2282-2288, 1932.
17. Hoobler, B. R.: J. A. M. A. 91: 307-310, 1928.
18. Hess, A. F.: Am. J. Dis. Child. 13: 98-109, 1917.
19. Sure, B.: J. Biol. Chem. 76: 685-700, 1928.
20. Dennett, R. H.: J. A. M. A. 92: 769-772, 1929.
21. Gaynor, M. F., and Dennett, R. H.: J. Pediat. 4: 507-513, 1934.
22. Elias, H. L., and Turner, R.: J. Pediat. 8: 352-362, 1936.
23. Price, Margaret R.: Brit. Med. J. 2: 80-82, 1940.
24. Clausen, S. W.: J. A. M. A. 104: 793-798, 1935.
25. Litchfield, H. R., Lichterman, J., Knoll, I., and Kurland, I.: Am. J. Dis. Child. 57: 546-553, 1939.

127 BAY STATE ROAD

122 SOUTH MICHIGAN BLVD.

## THE PERMEABILITY OF THE HUMAN PLACENTA TO WATER AND THE SUPPLY OF WATER TO THE HUMAN FETUS AS DETERMINED WITH DEUTERIUM OXIDE

L. M. HELLMAN, M.D., L. B. FLEXNER, M.D., W. S. WILDE, PH.D.,  
G. J. VOSBURGH, M.D., AND N. K. PROCTOR, M.S., BALTIMORE, MD.

*(From the Department of Obstetrics, Johns Hopkins University and Hospital, Baltimore, and  
the Department of Embryology, Carnegie Institution of Washington)*

IN A previous paper,<sup>1</sup> findings were presented on the permeability of the human placenta to sodium as determined with the radioactive isotope and the theory of the tracer technique in investigations of this kind was discussed. Our present concern is with the permeability of the human placenta to water, using deuterium oxide (heavy water) as the tracer substance. As in other studies from this laboratory, we shall analyze our data from the viewpoint of the following questions: (1) Does the permeability of the human placenta to water change with the period of gestation? (2) Is the permeability of the human placenta to water approximately like that of another member of the hemochorial group, the guinea pig, as is true for sodium? (3) What is the relative permeability of the human placenta to water and to sodium? (4) Does the human fetus, like the fetus of the guinea pig, receive quantities of water greatly in excess of the amount incorporated in growth?

### Method

Ninety-five per cent deuterium oxide ( $D_2O$ ) made isotonic with sodium chloride was injected into seven patients whose pregnancies were being terminated by the abdominal route at various periods of gestation and for various reasons, as shown in Table I. Sufficient  $D_2O$ , from 40 to 70 c.c., was used to give an estimated blood concentration at equilibrium of about 0.2 per cent. Since it was desirable to administer this amount as quickly as possible, the injection was made simultaneously into both antecubital or both anterior tibial veins. Complete injection required about thirty seconds; the beginning of the period of transfer to the fetus was counted from the time when half of the  $D_2O$  had been injected. The fetus was delivered and the umbilical cord clamped after a known interval, approximately ten minutes later.

There is a tendency for  $D_2O$  which has reached the fetus to be lost by re-entering the maternal circulation. If there is equal freedom in the movement of tracer back and forth across the placenta, it can be shown mathematically<sup>8</sup> that this loss will increase as the concentration in the fetus approaches that in the maternal plasma. To calculate the loss is a rather complicated process. It is simpler to use the criterion applied in the studies with  $D_2O$  in guinea pigs<sup>2</sup>: as long as the quantity of tracer (compared with the concentration in the maternal plasma) increases linearly with time, error due to backflow is minimal. Accordingly the human experiments, on the basis of the experience with guinea pigs, were limited to a transfer period of ten minutes.

In order to establish the rate of disappearance of  $D_2O$  from the blood after intravenous injection, successive samples of blood were taken at intervals up to

TABLE I. VALUES FROM WHICH THE DATA OF FIGS. 2 AND 3 AND TABLE II HAVE BEEN DERIVED. THE AVERAGE CONCENTRATION OF  $D_2O$  IN THE MATERNAL PLASMA FOR THE DURATION OF THE EXPERIMENT HAS BEEN CALCULATED AS EXPLAINED IN THE TEXT. DELIVERY TIME REFERS TO THE INTERVAL BETWEEN I. V. INJECTION OF  $D_2O$  AND CLAMPING OF THE UMBILICAL CORD

INDICATION FOR OPERATION	HISTORY NUMBER	GESTATION AGE WEEKS	DELIVERY TIME MINUTES	FETAL WEIGHT GM.	PLACENTAL WEIGHT GM.	TOTAL FETAL WATER C.C.	D <sub>2</sub> O IN FETAL WATER		D <sub>2</sub> O IN MATERNAL BLOOD WATER	
							PER CENT	FOUND	PER CENT	AVERAGE
Chorea	388120	14	9.0	58	92	53	0.180	0.330	0.330	0.617
Psychiatric	379368	16	10.5	113	44	100	0.172	0.240	0.449	0.449
Cardiac disease	376618	18	11.0	201	107	177	0.219	0.239	0.446	0.446
Chronic pyelitis	396381	31	10.8	1500	243	1215*	0.183	0.260	0.486	0.486
Previous section	311276	33	11.5	2100	370	1637*	0.142	0.174	0.325	0.325
Previous section	376433	37	13.0	3430	516	2459*	0.085	0.180	0.337	0.337
Contracted pelvis	408367	40	9.3	2490	335	1857*	0.054	0.220	0.411	0.411

\*Values in viable fetuses have been calculated from the volume of distribution of  $D_2O$ , and the concentration of  $D_2O$  in water obtained by vacuum distillation from a sample of blood.



one hour after injection of  $D_2O$  in three pregnant subjects. A sample of blood was obtained from viable fetuses two and one-half to three hours after delivery. The placenta was freed from excess blood, membranes, and cord; then weighed. The water from the maternal and fetal blood or from the total fetuses (when nonviable) was obtained by vacuum distillation to dryness at room temperature, condensation being carried out in tubes surrounded by dry ice and alcohol. It is essential that the distillation be carried to complete dryness because of the difference in the rate of vaporization of  $H_2O$  and  $D_2O$ . The water was next purified by passing it over  $CuO$  in a combustion furnace and distilling it from alkaline permanganate and chromium trioxide as described by Keston, Rittenberg, and Schoenheimer.<sup>3</sup>

The concentration of  $D_2O$  in the samples was determined by a modification<sup>3</sup> of the method of Barbour and Hamilton.<sup>4</sup> This consists of measuring, at an accurately maintained temperature, the falling time of a drop of water of fixed volume through a column of immiscible fluid of slightly lower density. M-fluorotoluene at a temperature of  $19.5^\circ C$ . was used as the immiscible medium. Other details of the method including the micropipette were as described by Keston, Rittenberg, and Schoenheimer.<sup>3</sup> Determinations on fetal water were run in duplicate, and checks to within plus or minus 0.01 per cent were obtained.

### Results

*The Disappearance Curve of  $D_2O$  From Blood After Its Intravenous Injection.*—The calculation of the placental transfer rate for water depends upon an accurate estimation of the average concentration of  $D_2O$  in the maternal blood for the period of transfer under observation. The reasons for this, and the method of obtaining the average value, are essentially the same as those previously presented for sodium<sup>1</sup> and need not be repeated in detail here. A known quantity of  $D_2O$  was injected intravenously into each of three pregnant women. The experimentally determined observations on the three individuals were all adjusted to an initial concentration of  $D_2O$  in the blood water of 1.3 per cent which about equaled the concentration anticipated from dilution of the amount injected by the calculated blood volume of the subject (see legend of Fig. 1). Since  $D_2O$  in plasma comes very rapidly into equilibrium with the red blood cells, water of whole blood was analyzed for its  $D_2O$  content. The disappearance curve of  $D_2O$  from the blood is given in Fig. 1. It is evident that the concentration in the blood declines rapidly during the first ten minutes and that equilibrium between blood and extravascular fluid is not reached for about twenty minutes. The average value for the concentration of  $D_2O$  in blood during the first ten minutes of the experiment is 1.87 times the concentration observed at the end of ten minutes; consequently the content of  $D_2O$  in the maternal blood samples obtained ten minutes after beginning the experiment must be multiplied by the factor 1.87 to give the average concentration of  $D_2O$  during the period of transfer.

*The Normal Placental Transfer Rate for Water at Different Gestational Ages.*—As has been previously discussed,<sup>1</sup> the quantity of water transferred to the fetus during the course of an experiment can be directly calculated from three quantities: the observed concentration of  $D_2O$  in fetal water, the average concentration of  $D_2O$  in the water of maternal blood, and the total volume of water of the fetus, on the assumption that there is no separation of isotopes. If these quantities be designated respectively by  $D_2O_f$ ,  $D_2O_{mb}$  and  $H_2O_f$ , then the quantity of water transferred to the fetus during the time of an experiment is equal to:

$$D_2O_f \times H_2O_f \div D_2O_{mb}$$

In the case of nonviable fetuses, total body water ( $H_2O_f$ ) was obtained from the

difference between the weight of the fetuses before and after vacuum distillation to dryness. In the case of viable fetuses, this quantity was secured by measuring the volume of dilution of a known quantity of  $D_2O$  injected intravenously into newborn infants,<sup>5</sup> and has the value of 74.6 per cent of body weight.

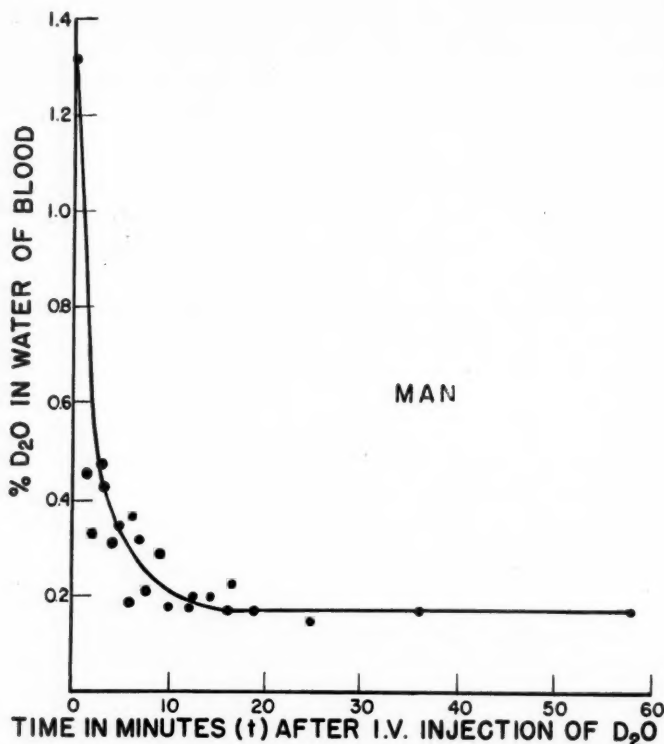


Fig. 1.—Change in concentration of  $D_2O$  in the water of the blood with respect to time. The measurements were made on three individuals, and observed concentrations of  $D_2O$  adjusted to an initial concentration of 1.3 per cent  $D_2O$ . To obtain the total water of the blood for calculation of the initial concentration of  $D_2O$ , we used the average volume per unit body weight of red cells in man as found by the radio iron technique,<sup>9</sup> the average volume of plasma given by the dye method,<sup>9</sup> and the water content of these two portions of the blood.<sup>10</sup>

The quantity of water transferred to the fetus per hour at various fetal ages is given in Fig. 2. It will be noted that the very large quantity of 3.6 liters of water per hour crossed the placenta to the fetus at the peak of the curve, which is at about the thirty-fifth week of gestation.

Using the values of Fig. 2 and Table I, the transfer of water per gram placenta per hour has been obtained by dividing the quantity of water transferred to the fetus in this time by the corresponding placental weight. These values are presented in Fig. 3. Although the cases are limited to seven, they describe a change in permeability entirely consistent with our rather large experience with sodium in man<sup>1</sup> and with several substances in animals.<sup>6, 7</sup> In view of this and the costliness of the deuterium oxide, we feel justified in basing our conclusions on this series of seven. Closely approximating the results with sodium, there is about a fivefold increase in permeability from the fourteenth week of pregnancy, the earliest case in the series, to the peak which occurs at about the thirty-fifth week. This peak in permeability at the thirty-fifth week is followed by a sharp decline to term.

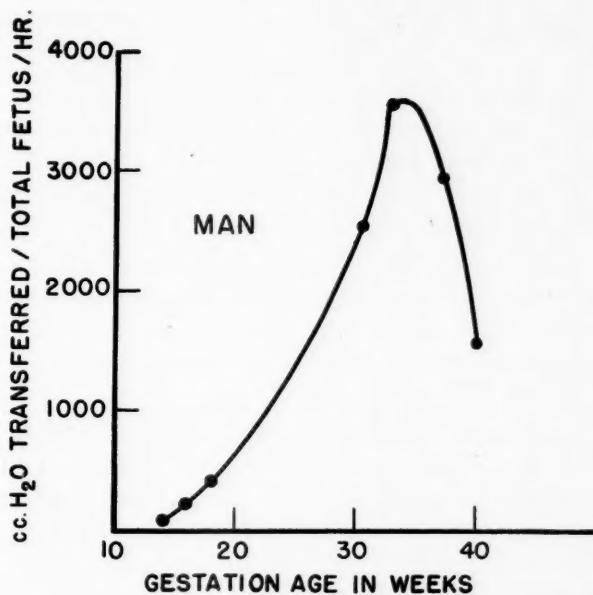


Fig. 2.—Variation of rate of transfer of water to human fetus with respect to gestational age.

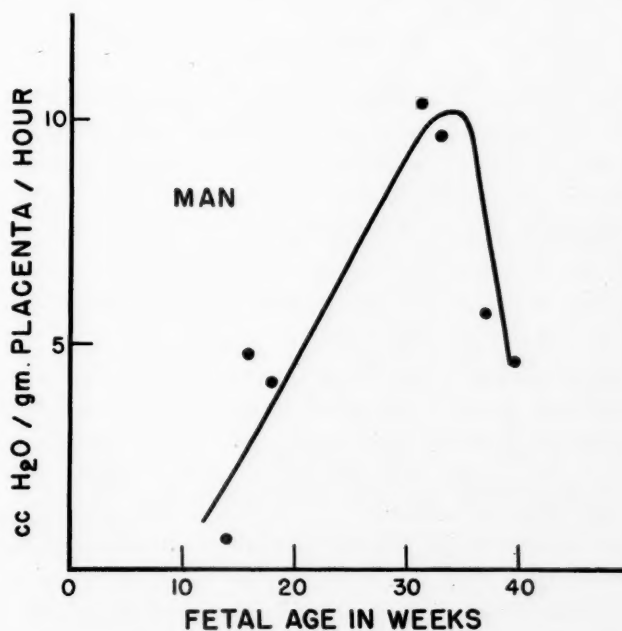


Fig. 3.—Variation of rate of transfer of water per unit weight of placenta with respect to gestational age.

*Fetal Need for Water Relative to Its Supply Across the Placenta.*—The ratio of the quantity of a substance supplied to the fetus from the maternal plasma to the amount of that substance retained by the fetus in its growth has been called the safety factor for that substance.<sup>1</sup> The quantity of water transferred per hour to the fetus across the placenta per hour is given in Fig. 2. The amount of water retained by the fetus in an hour's growth is equal to the fetal weight multiplied by the hourly per cent weight increase of the fetus multiplied by the total water in a unit weight of fetal tissue. The safety factor has been calculated for four fetal ages and is given in Table II. The value of the safety factor varies from 700 at a fetal age of fourteen weeks to the extraordinarily high value of 3,800 at thirty weeks. This means that of 3,800 parts of water delivered to the fetal circulation at thirty weeks, only one part is retained by the fetus in its growth and 3,799 parts are returned to the maternal circulation.

TABLE II. FETAL NEED FOR WATER RELATIVE TO WATER SUPPLIED ACROSS PLACENTA AT VARIOUS GESTATIONAL AGES. THE DAILY PER CENT WEIGHT INCREASE HAS BEEN CALCULATED FROM THE DATA OF STREETER<sup>11</sup>

GESTATION AGE	FETAL WEIGHT	DAILY WEIGHT INCREASE	TOTAL WATER CONTENT OF FETUS	TOTAL WATER TRANSFERRED TO FETUS PER HOUR	TOTAL WATER RETAINED IN HOURLY GROWTH OF FETUS	SAFETY FACTOR
WEEKS	GM.	PER CENT	C.C.	C.C.	C.C.	
14	58	6.4	53	101	0.14	720
16	113	5.3	100	207	0.20	1100
18	201	3.9	177	406	0.29	1400
31	1500	1.3	1215	2500	0.66	3800
40	2490	1.1	1857	1580	0.85	2000

### Discussion

The increase in the permeability of the placenta to sodium as gestation proceeds has been correlated with morphological changes in the placenta as it ages.<sup>1</sup> Variations in the permeability to water are similar to sodium and again it appears that thinning of the walls of the villi together with increase in area of placental exchange due to branching of the villi are fundamental factors underlying the increase in permeability. The terminal sharp decrease in placental permeability is probably due in considerable measure to the deposition of fibrin over the surface of the villus.

Striking correspondence has been observed in the permeability to sodium among four members of the hemochorial group<sup>1</sup>: at the middle of the ninth tenth of gestation in man, 6.5 milligrams of sodium cross a gram of placenta per hour; in the guinea pig, 6.1 milligram; in the rabbit, 6.8 milligrams, and in the rat, 8.3 milligrams. Water transfer has been studied only in man and guinea pig; the difference in the permeability of their placentas to water is greater than could have been predicted on the basis of the results with sodium. Thus, at the middle of the ninth tenth of gestation about 10 c.c. of water cross a gram of the human placenta per hour, whereas about 20 c.c. of water cross a gram of the placenta of the guinea pig per hour. The meaning of this difference from the viewpoint of comparative physiology cannot be appraised without information on other members of the hemochorial group as well as representa-



tives of the other morphologic types of placenta. It serves as an example, however, of the uncertainty of making precise predictions about the behavior of one substance (in this instance water) from the behavior of another substance (in this instance sodium) among animals of the same or different types of placentas.

It is our purpose to characterize the placenta on the basis of its relative permeability to as many of the constituents of the maternal plasma as is possible. When this is accomplished, we shall be in a position to attempt to relate the physico-chemical properties of these substances to the rate at which they cross the membrane and to gain an insight into the forces which govern placental transfer. If the concentration of a normally occurring substance in the maternal plasma be designated as  $C_{mp}$ , the total quantity of this substance transferred to the fetus during the time,  $t$ , as  $Q_t$  and the weight of the placenta as  $W$  ( $W$  is taken to be proportional to the area of the transfer surface) then:

$$Q_t = kWC_{mp}t$$

in which the amount of substance transferred to the fetus in a certain time is assumed to be directly proportional to the concentration of the substance in the maternal plasma, to the weight of the given placenta, and to the length of the period of transfer. It is evident that the greater the apparent permeability of the placenta to a given substance, the larger will be the value of  $k$ .

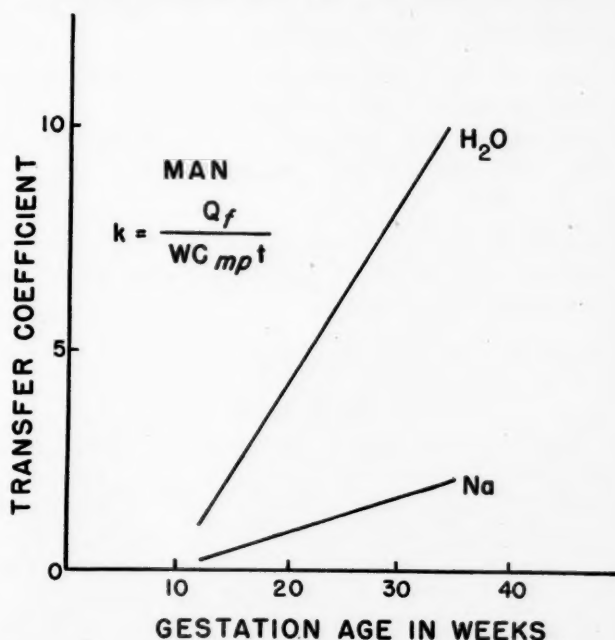


Fig. 4.—Placental transfer coefficient for water and sodium at various gestational ages. The coefficient is defined in the text.

The coefficient  $k$  is influenced by many factors. It probably depends upon the permeability of the placenta, i.e., the characteristics of the placenta as a membrane, the presence or absence of secretory activity by the placenta with respect to the substance and the physico-chemical characteristics of the substance. If it were certain that the placenta performs no secretory work in the transport

of material across it and so acts as an inert membrane,  $k$  could properly be designated the permeability coefficient. Since the mechanism of transfer is unknown, it appears preferable to designate the coefficient as the transfer coefficient and so to avoid implication as to the precise nature of transfer.

The transfer coefficient for water and sodium as functions of gestational age are given in Fig. 4. The value for water is about five times that for sodium from the twelfth to the thirty-fifth week of gestation, i.e., the human placenta appears to be five times as permeable to water as to sodium. The difference in the behavior of water and sodium may be due to secretory activity by the membrane or to the physical characteristics of the membrane which permits water to pass through it more readily than sodium. Differences of this kind have been observed in a study of the relative rate of passage of water and sodium from the inside to the outside of a collodion sac.<sup>2</sup> No deductions, consequently, can be made about the nature of placental transfer from the difference in apparent permeability to sodium and to water.

### Summary

1. Changes in permeability of the human placenta to water have been measured with deuterium oxide as the tracer material from the fourteenth week of pregnancy until term. There is about a fivefold increase in transfer rate of water per unit weight of placenta during this period.

2. The placental transfer coefficient for water is five times as great as that for sodium at corresponding periods of gestation.

3. The permeability of the placenta of the guinea pig to water has been found to be about twice that of the human placenta; this divergence is considerably greater than for sodium.

4. The human fetus receives across the placenta at the fourteenth week of gestation 700 times and at the thirty-first week 3,800 times as much water as is incorporated in the growing tissues.

The heavy water used in these experiments was kindly supplied by the Abbott Laboratories.

### References

1. Flexner, L. B., Cowie, D. B., Hellman, L. M., Wilde, W. S., and Vosburgh, G. J.: *AM. J. OBST. & GYNEC.* 55: 469, 1948.
2. Gellhorn, A., and Flexner, L. B.: *Am. J. Physiol.* 136: 750, 1942.
3. Keston, A. S., Rittenberg, D., and Schoenheimer, R.: *J. Biol. Chem.* 122: 227, 1937.
4. Barbour, H. G., and Hamilton, W. F.: *Am. J. Physiol.* 113: 135, 1935.
5. Flexner, L. B., Wilde, W. S., Proctor, N. K., Cowie, D. B., Vosburgh, G. J., and Hellman, L. M.: *J. Pediat.* 30: 413, 1947.
6. Flexner, L. B., and Gellhorn, A.: *AM. J. OBST. & GYNEC.* 43: 965, 1942.
7. Wilde, W. S., Cowie, D. B., and Flexner, L. B.: *Am. J. Physiol.* 147: 360, 1946.
8. Wilde, W. S., Scholz, R. O., and Cowie, D. B.: *Am. J. Ophthalmol.* In press.
9. Gibson, J. G., Peacock, W. C., Seligman, A. M., and Sack, T.: *J. Clin. Investigation* 25: 838, 1946.
10. Peters, J. P., and Van Slyke, D. D.: *Qualitative Clinical Chemistry* 1: Baltimore, 1931.
11. Streeter, G. L.: *Contrib. to Embryol. Carnegie Inst. Washington* 11: 146, 1920.

## PUERPERAL PERIGENITAL AND PERINEAL HEMATOMAS\*

FRANK J. WALSH, M.D., AND HOWARD I. GANSER, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, St. Elizabeth's Hospital)

**P**UERPERAL perigenital and perineal hematomas are accumulations of blood in the perigenital soft connective tissue resulting from the rupture of a blood vessel, usually a vein, incumbent on the trauma of labor. Blood escaping into the soft connective tissue tends to follow the planes of cleavage of the fascia, and when this process occurs high in the genital tract, the blood tumor forms in or below the broad ligaments, in the perivesical space, or beneath the vesico-uterine fold of peritoneum. These hematomas tend to dissect under the peritoneum and may extend upward under the inguinal ligament or posteriorly to the region of the kidney or the diaphragm. A hematoma occurring in the perivaginal region or the lower part of the birth canal forms a blood tumor that may close the vagina, distend the vulva and perineum, or displace the rectum or the urethra.

Such a complication usually occurs during the descent of the fetus or shortly after delivery. However, it has been reported by Frank-Kamenetsky<sup>1</sup> that a large hematoma, forming after the first twin, caused obstruction to the delivery of the second (in four cases), and that it is possible for a large tumor to form an obstruction to the delivery of the placenta.

DeLee-Greenhill<sup>2</sup> state that cases have been reported as late as twenty-one days post partum, and Lamm and Lamm<sup>3</sup> recently reported a case occurring fourteen days post partum.

### Incidence

The incidence of occurrence varies greatly. DeLee-Greenhill<sup>2</sup> state that they found an over-all incidence of one in 4,000 cases, but that large hematomas occurred only seven times in the pathologic work of 70,000 cases, or 1:10,000. Michaels and Herring,<sup>4</sup> of New Orleans, report one in 5,474 cases, Williams<sup>5</sup> reports one in 2,000 cases, while Moshkow<sup>6</sup> has an incidence as low as one in 1,951 cases. One of the factors responsible for the discrepancy is, of course, the fact that frequently the tumors are small and insignificant or undiagnosed. In 1940, when Hugh Hamilton<sup>7</sup> reviewed the literature, he was able to find only 156 cases, including twelve of his own. Since that time, eight new cases have been reported in the United States literature.

### Etiology

The etiologic factor is primarily trauma resulting in the bursting of a blood vessel. In the delayed type, pressure necrosis is the injury that results in delayed blood loss. This cannot be the entire story, however, as too many of

\*Presented before the 588th regular meeting of The Chicago Gynecological Society, Oct. 17, 1947.

these cases occur in the absence of evident trauma and in spontaneous deliveries following easy labors. It has been observed that toxemia predisposes. This is possibly on the basis of vascular changes that accompany albuminuria and hypertension and that may account for retroplacental hematoma with abruptio placentae. Most cases occur in primiparas (59 per cent of the cases reviewed by Hamilton), but some of the most extensive damage has been seen in multiparas, as in our first and third cases. Another suggested factor is increased fragility of the vessels and hemorrhagic tendencies associated with constitutional diseases. In discussing Hamilton's paper in 1940, W. H. Rubovits told about a case of his that developed postpartum bleeding from the upper end of an episiotomy that was very difficult to control. After recovering from this, the patient died from hemorrhage at the back of the tongue that started from no more trauma than a passionate kiss. There are several cases reported that show bleeding at sites other than the pelvis, such as epistaxis and retinal hemorrhages.

There is a great deal of discrepancy of opinion as to the role played by varicosities of the veins in the perigenital region. In our first case, it is possible that they were a contributing factor. If a normal vessel can be accused of rupture, then we fail to see any defense for an already injured one. DeLee-Greenhill<sup>8</sup> state that rupture of a varix in the broad ligament is one of the causes of obstetric shock.

Surgical repair of episiotomy or laceration may be a causative factor if a large vein or varicosity is pierced during the repair. Hematomas thus formed are seldom of consequence, as they are noted and tended to immediately or are small and resorb spontaneously. One reported case is ascribed to failure to secure hemostasis during the repair of the episiotomy.

### Symptoms

The symptomatology is primarily pain and/or blood loss. Although the pain of tearing of the tissues during the formation of the hematoma is usually excruciating and forces the attendant to search out the cause, our third case developed the largest hematoma that we have seen and complained of pain only on motion. E. G. Lipow<sup>9</sup> reports a case associated with rupture of perineal muscles with exacerbation of the pain at the time of rupture of each muscle. As large amounts of blood can be lost, the picture of anemia and shock is readily understandable.

### Findings

The findings vary with the type of hematoma. Those that appear on the perineum or vulva are readily seen. Those limited to the vagina, however, have to be searched out with a speculum. Both appear as a tense, bluish, fluctuating mass that may have abraded or weeping surfaces. Those that occur above the cardinal ligaments have to be palpated bimanually or rectovaginally.

### Differential Diagnosis

In the differential diagnosis, one must consider:

1. *Inversion of the Uterus*.—This can be ruled out by the absence of the uterus in the abdomen or pelvis, with notching at the attachment of the broad ligament, and manual definition of the tumor mass appearing in the vagina.
2. *Prolapse of the Cervix or Vagina*.—This can be definitely identified by careful inspection and the absence of pain and shock.
3. *Threatened Rupture of the Uterus or Rupture of the Uterus While the Baby Is Being Extracted*.—Bimanual and intrauterine examination will readily lead to a diagnosis.



4. *Obstetric Shock*.—A hematoma above the cardinal ligaments, due either to the rupture of a varix in the broad ligament or to pressure necrosis, must be kept in mind and looked for in all cases of so-called obstetric shock.

### Treatment

Historically, the treatment of perineal hematomas was expectant. If or when infection occurred, that was the indication for drainage and evacuation of the cavity. This type of management led to many deaths on the basis of sepsis. The next step was the evacuation of the blood as soon as thrombosis was complete, in about forty-eight hours, with the end in view of preventing the sepsis, but waiting long enough to reduce the possibility of secondary hemorrhage. Some men adhere to this type of management. The consensus at present, however, is to evacuate the blood, secure hemostasis of large vessels by ligature or suture ligature, and pack the cavity. In this way, it is conceivable that the dissection along the planes of cleavage be interrupted before the patient suffers the full damage. Light packing of the hematoma cavity, with further tight packing of the vagina and binding of the perineum, seems to yield the best results. Perhaps it would be satisfactory to pack the cavity with hemostatic absorbable sponges.

When dissection is above the cardinal ligaments or the hematoma is limited to the perimetrium, laparotomy is indicated, and hemostasis must be secured in the most effective manner, so that the area is dry before closing of the abdomen. Hysterectomy is frequently necessary.

Of course, supportive therapy, especially the replacement of blood loss, is imperative.

### Case Reports

CASE 1.—Mrs. C. N., a 36-year-old, white, gravida vii, was admitted to the hospital Dec. 21, 1945. She had had adequate prenatal care and was admitted at term with moderate pains but no progress. In three hours, the pain had become exceedingly severe, and the obstetrician was called in consultation. Examination at that time revealed a patient screaming like a wounded animal, with an ashen face and a slow pulse of good quality. The bladder appeared greatly distended. The position and presentation were bregma right anterior (shown on previous x-ray), fetal heart tones were 150, the bag of waters was bulging and seemed to be under great pressure, the cervix was fully dilated, and the station minus three. A diagnosis of threatened rupture of the uterus was made, and immediate delivery was recommended and carried out as follows: The patient was anesthetized, the bag of waters was ruptured, the head was flexed, and in two or three pains the patient pushed the head into the pelvis, where it could be delivered easily with forceps.

Immediately following the delivery of the baby there was a large bright red clot of about 200 c.c. The ergotrate was given, and the placenta was delivered by simple expression. The patient continued to bleed bright red blood in spite of a hard uterus and an intact cervix. Bimanual examination revealed a large, soft mass, tense and fluctuating, above and anterior to the bladder. The vagina was tightly packed, and the patient was taken to surgery for laparotomy. Shock therapy and replacement of blood were started immediately. At laparotomy, the following were seen: A large hematoma, the size of a grapefruit, on top of the bladder and under the vesicouterine fold of peritoneum; a postpartum uterus about 14 cm. long, and many large varicosities of the right broad ligament. The area of the uterus posterior to the bladder appeared soft, edematous, and infiltrated with hemorrhage. The hematoma was evacuated, and a supracervical hysterectomy was performed. Hemostasis required more than the usual number of sutures; however, the peritoneum was preserved and used in the usual manner over the stump. The postoperative course was uneventful, and the patient was discharged on the thirteenth postoperative day, in good condition.

The interesting features of this case are the question of diagnosis and the pathogenesis of the hematoma. The early picture of threatened rupture naturally put the operator in mind

of a small rupture immediately post partum, but the equivocal findings did not conform to the impression. However, the specimen in situ looked like a small rupture after the hematoma was removed from the uterus. Only after the uterus was removed was it determined that no rupture existed. The sections did show hemorrhage infiltrating the myometrium, which was so obviously damaged in the gross specimen.

The suggestion of the etiology of the hematoma is the other point of interest. The persistent bregma incarcerated the lower uterine segment and the bladder between it and the symphysis pubis and mashed this tissue under the pressure of the uterine contractions. This is similar to the mechanism of a colporrhaxis when the occiput is directed against the sacral promontory as in a case of pendulous abdomen.

We believe the management of this case terminated the pathologic mechanism while the damage was only a hematoma and threatening rupture of the uterus. We believe the failure to interfere would have led first to an incomplete and then to a complete rupture of the uterus. The forces which ruptured the vessels and led to the hematoma are the same that, if prolonged, can rupture the uterus.

CASE 2.—Mrs. M. T., a 36-year-old, white primipara, was admitted to the hospital on June 15, 1947, in active labor. She had had adequate prenatal care. Although every attempt was made to limit this patient's diet, she persisted in overeating and gained 46 pounds. In the last three weeks of her prenatal period, she developed a low-grade toxemia, with a blood pressure at times up to 140/100 and albuminuria of from 20 to 50 mg. There was a moderate degree of water retention and edema of the feet and legs. She was admitted to the hospital eight days before her expected date of confinement and was found to have a blood pressure of 140/100. The position was right sacrum anterior. The fetal heart tones were 140, and she was in active labor, with pains occurring every four minutes, of moderate intensity and lasting thirty seconds.

She was given sedation, and labor progressed rapidly. In three and one-half hours, she delivered with manual aid and a left mediolateral episiotomy a six pound, five ounce female infant.

During the repair of the episiotomy a hematoma about 4 cm. in diameter was noted in the left vaginal wall, about 3 cm. above the top of the incision. During a period of observation, the hematoma was seen to be self-limiting. It was incised and the clots evacuated, but as there was no active bleeding, packing was deemed unnecessary. She was given chemotherapy in an attempt to avoid infection. On the fifth postpartum day, however, she developed a low-grade fever and discharged a few dark clots per vagina. The fever and discharge resolved by the eleventh postpartum day, and the patient was discharged on the thirteenth postpartum day in good condition. She had no further difficulty, and at the six weeks' postpartum examination no scar could be found in the vagina, and involution was complete.

CASE 3.—Mrs. A. V., a 30-year-old, white, gravida iii, para 0, was admitted to the hospital on March 29, 1947. Prenatal care was adequate. She was given progesterone in the first half of this pregnancy because her previous obstetric history consisted of one spontaneous abortion and one miscarriage at five months of a twin pregnancy. There was no evidence of toxemia. She was admitted to the hospital in active labor with a blood pressure of 110/68, with occiput left anterior, fetal heart tones 138, pains regular and of moderate intensity. Sedation was given, and labor progressed normally, and after thirteen hours and fifteen minutes, following a left mediolateral episiotomy, she delivered spontaneously a six pound, three ounce female infant. The episiotomy was repaired, and the mother was sent to the floor in good condition.

Fourteen hours later, the patient complained of pain in the perineal region on motion. Examination revealed that she was cool, moist, and cyanotic, with a pulse of 120 to 130. A huge hematoma, involving the right side of the labia, vestibule, perineal body, and both buttocks, was found. Immediate treatment consisted of treating the shock and replacing the blood loss. The clots were subsequently evacuated, and, as no bleeding was seen at this time, the hematoma was left to granulate. In the early stages, penicillin and sulfadiazine were

given to prevent infection of the cavity. When the surfaces showed good, clean granulation, a secondary closure was attempted on the twenty-fourth day post partum, but was only partially successful. It did accomplish, however, the bridging of skin and mucous membrane in some places and shortened the time necessary for epithelialization.

The wound was completely healed in forty-five days, although hospitalization was not required for the full time. The patient has a functional perineum without complaints, but, as further childbearing is contemplated, plastic will be delayed.

### Summary and Conclusions

1. Three cases of postpartum perigenital hematomas are presented: one perineal, one vaginal, and one supravaginal.
2. The etiology, pathogenesis, and diagnosis are discussed.
3. A historical review of the treatment is given, and the modern local treatment is discussed.
4. Early incision of the hematoma with ligature or suture ligature of large vessels and packing of the hematoma cavity is the treatment of choice for perineal or vaginal hematomas, while laparotomy is indicated in the supravaginal variety, and hemostasis must be secured before closure of the abdomen, even if a hysterectomy is necessary.

25 E. WASHINGTON STREET.

### References

1. Frank-Kamenetsky: *J. Obst. and Gynaec. Brit. Emp.* 17: 121, 1910 (Review).
2. DeLee, J. B., and Greenhill, J. P.: *Principles and Practice of Obstetrics*, Philadelphia, 1943, W. B. Saunders Co., pp. 769-770.
3. Lamm, A. T., and Lamm, H.: *Texas State J. Med.* 38: 276-277, 1942.
4. Michaels, J. P., and Herring, J. S.: *New Orleans M. and S. J.* 95: 37-39, 1942.
5. Williams, J. W.: *Surg., Gynec. & Obst.* 21: 541, 1915.
6. Moshkow, B. N.: *Monatschr. f. Geburtsh. u. Gynäk.* 92: 421, 1932.
7. Hamilton, H. G.: *AM. J. OBST. & GYNEC.* 39: 642-648, 1940.
8. DeLee, J. B., and Greenhill, J. P.: *Principles and Practice of Obstetrics*, Philadelphia, 1943, W. B. Saunders Co., p. 827.
9. Lipow, E. G.: *AM. J. OBST. & GYNEC.* 42: 1077-1080, 1941.

### Discussion

DR. D. N. DANFORTH.—The subject which Dr. Walsh has presented is one which very fortunately is rarely encountered in practice. Its importance, however, is attested by the occasional reports of fatality due to this cause. The active treatment which he has outlined seems very adequate. Two points which he has mentioned I think are deserving of greater emphasis. First is the early diagnosis. The only case of massive hematoma I have seen, one which extended to Poupert's ligament and deep into the left buttock, occurred in a woman who had complained bitterly of "painful stitches" for twelve hours before an adequate rectal examination was made. The second point, which I consider of the greatest importance, is prevention. In the past five years at the Evanston Hospital, there have been twelve postpartum hematomas which were sufficiently troublesome, or large enough, to be dignified by this diagnosis. During this period there were 6,890 deliveries, giving an incidence of 0.6 per cent. Ten hematomas were perineal. None were of the massive type described by Dr. Walsh, although in three cases they were sufficiently large that the mass was incised and evacuated. In one of these, as in Walsh's third case, the accumulation of blood was very obviously due to defective hemostasis at the time of delivery. All of the perineal group were febrile, the elevation first appearing between the third and fifth postpartum days. This was of a low-grade type, reaching up to 101° F. Its consistency in these cases suggests that fever is an important part of the clinical picture, and suggests further that a careful rectal examination may be useful in the diagnosis of unexplained fever during the puerperium.

Two of the cases were of the broad ligament type. In one of these, fever and the presence of a broad ligament mass were noted on the fourth postpartum day. The mass gradually began to subside, and the patient was discharged in good condition on her sixteenth postpartum day. The other broad ligament case was more colorful. The patient was a multipara. A Pituitrin induction was done, employing an initial dose of 3 minims, followed by a second dose of 3 minims, and a third dose of 2 minims. The length of labor was three hours. The patient sustained a high left cervical laceration. This was repaired and a vaginal tamponade inserted. Two hours later a grapefruit-sized hematoma of the left broad ligament was evacuated by laparotomy. The patient made an uneventful recovery. It seems likely that this accident might not have occurred if smaller dosage of Pituitrin had been employed, namely, an initial dose of  $\frac{1}{2}$  minim followed if necessary by 1 minim at intervals of 30 minutes.

Dr. Walsh mentioned the importance of proper hemostasis at the time of delivery in the prevention of postpartum hematomas. Cervical tears, irrespective of length, may give rise to only modest external bleeding. It is curious that in only two of the seven maternity hospitals in which I have worked in the last eight years is it part of the obstetric routine in all cases to inspect the cervix following delivery. Yet, in a series of some 3,500 consecutive deliveries reported from the Evanston Hospital in 1936, in 6.3 per cent of the cases there were lacerations which were 3 cm. or more in length. In addition to restoring the functional integrity of the cervix, it is possible that immediate cervical repair might have a bearing upon the later development of high incidence of hematomas.

Despite the possibility of late necrosis, or intrinsic defect in the blood vessels of the perineal area as a cause of hematomas in this region, it seems inescapable that the vast majority result from improper hemostasis at the time of the repair. I wish to show a lantern slide of a method for the repair of episiotomy which answers this objection. Lifting ligatures are employed to make the supporting structures stand out, and the vaginal fingers press the repaired vaginal mucosa toward the operator. By this means the depth of the incision is made easily accessible.

I enjoyed Dr. Walsh's presentation, and believe the subject is deserving of more consideration than it has received in recent years.

DR. W. H. RUBOVITS.—The same general surgical principles usually employed will simplify the matter of prevention and treatment of this type of hemorrhage. By that I mean, that the attitude toward cervical hemorrhage, whether it be obstetric or gynecologic, is much the same. It is self-evident that hemorrhages of the kind described by the essayists are certain to occur but similar hemorrhages occur in most mysterious ways in gynecologic work. In those days when we did more supravaginal hysterectomies, hemorrhages occurred from the cervical stump in a most inexplicable manner and, also, from the vaginal cuff in total hysterectomy. Hemorrhages from these very vascular structures do occur in the operative care of intraligamentary tumors, particularly fibroids, and it is striking that many of these are formidable-looking tumors and shell out of the intraligamentary folds with little or no hemorrhage, whereas operative fatalities in apparently similar cases occur, due to the predisposition of the patient to bleed from some apparent blood dyscrasia or "pseudohemophilia." With these thoughts in mind, I have tried to concentrate on the matter of hemostasis. Our slogan is, it is easier to save blood than to transfuse. It is easier to check bleeding now at the time of delivery or at the time of operation than it will be twelve hours from now. To that end, and finding it difficult often to employ a suitable needle holder in an inaccessible area, such as the extension of an episiotomy into the fornix, involving a large branch of the uterine artery, I use the Deschamps sharp suture carrier. If there is danger to the urinary bladder, it is possible to make a transverse incision, push the bladder out of the way, and by retracting it, and the ureter, one can very quickly use this instrument for the ligation of the formidable bleeding vessel.

DR. WALSH (Closing).—In our third case, the woman with the severe hemorrhages, I believe, had some type of blood dyscrasia. We rechecked but found nothing except that she ran a low-grade anemia.



## **A CLINICAL STUDY OF NATURAL CHILDBIRTH**

### **A Preliminary Report From a Teaching Ward Service**

FREDERICK W. GOODRICH, JR., M.D., AND HERBERT THOMS, M.D.,  
NEW HAVEN, CONN.

*(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)*

**I**T IS not unusual for obstetricians to attend women in labor who have appeared to experience little or no distress. This often is explained on the grounds of stoicism, high multiparity, or high pain threshold. Since the advent of anesthesia great emphasis has been placed on the alleviation of pain in labor, and pain itself has come to be accepted as a normal concomitant. Most obstetricians, however, will agree that emotion does play a large role in pregnancy and labor, and that the woman who is anxious, fearful, and tense at the start of labor will not go through that performance as well as one who has a sympathetic understanding of the situation and accepts it more or less philosophically. In considering this subject, attention must be given to the work of Dr. Grantly Dick Read, of London, who, through his writings and teaching, not only has given an explanation of the cause of pain in childbirth, but has also suggested methods for its prevention in normal labor. He points out that the inner circular muscle layer of the uterus is innervated by the sympathetic nervous system and that it acts as a sphincter in much the same manner as the bladder sphincter. This sphincter action is opposed in the uterus, as in the bladder, by the action of the longitudinal or detrusor muscle, which is innervated by the parasympathetic nervous system. If for any reason the circular sphincterlike muscle and the longitudinal muscle are contracting at the same time, the intrauterine tension will reach a threshold at which the impulses transmitted through the thalamus to the cortex will be interpreted as pain. In physiologic labor this should not occur except possibly at the end of the first stage, when the stretching of the cervix is at its maximum.

Physiologic investigations have shown that in general sympathetic discharge occurs in a state of fear. Fear can cause tension, which in itself causes pain. That fear, to a greater or lesser degree, is present in labor almost universally in our culture is not surprising when we consider the fact that the young woman approaching childbirth not only has acquired a mass of misinformation concerning childbirth, but has also acquired a belief that labor is a painful and terrifying ordeal. This fear usually grows concurrently with the abdomen. One example of this attitude was expressed by one of our patients who, after a natural labor, exclaimed, "Now I know what it is like, I can have another baby without being afraid!"

In the usual conduct of labor the obstetrician attempts to break the fear-tension-pain syndrome by drugs which will produce analgesia or anesthesia, or

both. Those who advocate the psychological approach to the problem believe that the cycle can be more rationally interrupted at the place where it begins, in fear, and that this can be done by education. Obviously this may not be easy, because a fear which is part of an environmental pattern may be difficult to dispel. Nevertheless, in most women such fear can be reduced so that pain and discomfort can be eliminated to a degree that a woman is willing and able to accept. In our study we have delivered five women who have steadfastly denied on repeated questioning that they felt anything which could be classified as discomfort. These women were alike only in that they appeared completely fearless during labor.

To state the hypothesis briefly, traditional fear is manifested in labor by tension, and tension generalized and specific is the chief cause of pain in normal labor. Whether this assumption is scientifically correct from the viewpoints of anatomy, physiology, and psychology is not too important if it can be accepted pragmatically. Our experience has taught us that it can, for it works.

Shortly after publicity was given in the lay press to Dr. Grantly Dick Read's work, a young primigravida was admitted to our ward, early in labor, who announced that she wanted natural childbirth without anesthesia. She was completely successful in achieving her desire, much to the great interest of those who attended her. It was not long before other clinic patients expressed a similar desire, an interest which we were glad to encourage. In the six months following the first demonstration we delivered sixteen such women, and the experience was enough to convince the professional and nursing staff that natural childbirth was a very real thing and that it demanded more than casual consideration.

Since an unusual patient-physician relationship seemed to be a primary requisite, and since the technique as described by Dr. Read apparently required a high degree of cooperative intelligence on the part of the patient, we were anxious to determine whether these principles could be applied in a teaching ward obstetric service. It was decided, therefore, to select for study every third patient who registered in the clinic, provided she was no more than twenty-eight weeks pregnant and was deliverable from below. We proposed to apply to this selected group the physiotherapeutic and psychological techniques recommended for natural childbirth. In addition, it was decided to include in the study, also, those women who came to the clinic requesting natural childbirth.

We outlined the procedure to be adapted to these two groups and, in addition to the usual prenatal program, put into operation a conditioning program which is essentially of a dual nature. One aspect of this might be termed the elimination of negative conditioning, and the other the substitution of positive conditioning. The former consists of attempting to change the attitudes and behavior patterns traditional not only in pregnant women, but in hospital attendants of women who are delivered on a teaching ward obstetric service. For example, we have eliminated from our vocabulary the word "pain," always speaking of "contractions." Positive conditioning consists of those procedures which are used in educating the expectant mother to the end that she will enter the labor with an assurance that she is undergoing a normal experience and that

she will be aided by sympathetic and skilled attendants in whom she can have complete confidence. All of the patients in the study, "selected" or "volunteer," are treated essentially as follows. The registration or initial visit follows the usual pattern of history taking, physical examination, laboratory study, and instruction. In addition, an attempt is made to assess the patient's personality, to reassure her as to her physical condition, and to make her feel that the clinic staff of nurses and physicians is taking a real interest in her. She is encouraged to ask questions. On the following visit, in addition to the routine antenatal examination, the patient attends a short lecture on the anatomy and physiology of the female genital tract, information about fertilization, fetal growth, and the explanation of the signs and symptoms of early pregnancy. Patients are told about the effects of tension and the relationship of fear to tension and pain. Diagrams are used as much as possible, and questions are encouraged. During the next visits the patient is taught four exercises which are designed to increase the elasticity and tonus of the back, abdominal, and perineal muscles, and also breathing and position exercises which aid in relaxation. Shortly after inaugurating the program, through the generosity of the Maternity Center Association of New York, we were fortunate in having with us for a short period Mrs. Helen Heardman, of England, a skillful physiotherapist who for the past eight years had been working with pregnant and parturient women. Under her teaching we learned the exercises which are now taught by the physician in charge of the follow-up prenatal examination. This instruction is augmented by classes conducted by a nurse midwife who has been trained also in the use of these physiotherapeutic techniques. Patients are instructed to practice these exercises of regular intervals at home.

At the first visit in the eighth calendar month patients attend a second lecture on the course of labor. The action of the muscles concerned in labor is outlined, the various stages of labor are explained, and the role that the patient should play in each period is explained. Patients are also told about the signs and symptoms of early labor and the hospital admitting routine. At no time during any lecture is the patient told that labor will be painless or that she will receive no anesthesia. Following this second lecture the patient will ordinarily come for about four more clinic visits before delivery. During these she attends exercise classes conducted by a nursing supervisor or a nurse midwife. Mistakes are corrected and labor is rehearsed. Breast massage is started for those who intend to nurse their infants.

If the patients have been properly indoctrinated by this regime, the effect is obvious on their admission to the hospital. They appear calm, confident, and quite ready to undergo an experience which to them seems to be a natural one.

The management of labor in these patients follows a rather definite pattern. We attempt to follow several principles. The *first* is that of keeping the patient informed of her progress. She is told about the position of her baby. She may listen to the fetal heart, and she is informed from time to time of the progress of the baby through the birth canal. The devious explanation, the hushed tones, or the overly sympathetic attitude are studiously avoided. *Second*, the patient is

not allowed to be alone. Again, through the good auspices of the Maternity Center Association, we are fortunate in having the services of a nurse midwife on our ward service who has been trained in these methods, and she or the regular nursing supervisor, or a delivery service nurse, is with the patient. The physician also sees the patient at proper intervals, especially during certain important periods in the labor. *Third*, the techniques of relaxation are instituted when they become necessary. This usually occurs in the average labor when the external os reaches about 4 cm. dilatation. Ordinarily up to this point the patient is hyperactive and may be mildly euphoric. However, the contractions at this period are apt to be stronger and relaxation techniques usually become necessary. If used too early, these techniques may become tiring in themselves because of the concentrated mental effort necessary to carry them out. At this stage, when the patient assumes the relaxing position and starts abdominal breathing, it is easy to demonstrate to her the effect of such relaxation by the alleviation of her discomfort. This reinforces her confidence and more often than not will allow her to continue to nearly full dilatation without further instruction. When almost full dilatation is reached, the most crucial point in the labor is at hand. The physician should certainly be present at this time. Concurrent with an increased amplitude of the contractions, the patient may complain of a severe backache. This can be relieved by an attendant giving pressure and massage over the sacral region. In addition, the patient needs reassurance that all is going well and that after ten or twelve contractions she will feel better, which actually occurs when the second stage becomes established. When the second stage is started the patient is urged to work with her contractions and to relax between times. As the labor progresses the patient is encouraged to assume a more mechanically advantageous position, which consists in flexing the thighs on the abdomen and the legs on the thighs. The patient is aided in this by attendants, and in this way simulates the squatting position which she has learned in her class work. When the contraction fades away she straightens out her legs and again relaxes. The patient is not placed on the delivery table until delivery is assumed to be about ten or fifteen minutes distant, and she is not placed in stirrups until the last possible moment. Many patients have told us that the position in stirrups destroys the mechanical advantages of the fully flexed position.

We use episiotomy when indicated in primigravidas and multiparas. This can be done in many instances without disturbing the patient at the acme of a contraction, when the head distends the perineum. Patients may not even be aware of its performance. However, infiltration with a local anesthetic may be useful, especially later on during the repair of the incision. As the head is being delivered over the perineum the mother is asked to pant, which she does with ease, and the head is delivered slowly. After the delivery the infant is placed on the sterile drape covering the abdomen and at this point she usually becomes quite euphoric. However, sterile technique is maintained and she is not allowed to touch the baby except through the drapes. When the placenta separates, the mother can usually deliver it without aid. Bleeding is usually minimal, and the third stage is generally very short. As may be expected, the necessity for the use of methods of resuscitation for the infant is so rare as to be practically nonexistent.

Since our study of these methods has been in operation but a relatively short time, the total number of women who have been delivered is limited. At this writing we present a total of 156 deliveries. We feel, however, that our observations in this number have enabled us to reach conclusions that are significant. It is obviously difficult in a study of this nature to be completely objective. Many of the factors which we are attempting to evaluate cannot be measured.



By means of special records, however, we have attempted to evaluate our results from many points of view. We have tried to study certain aspects of the personality of these patients, to record the indoctrination that they receive, their reaction to it, and to assess the emotional reaction to labor as well as the physical response.

The classification of the end result has been arbitrarily divided in the following grouping:

1. Those labors in which the mother does not ask for or appear to need analgesia or anesthesia are classified as *excellent*.

2. Those labors in which the mother receives a minimum of medication or anesthesia, either because she requests it or seems to need it, are classified as *good*. By minimum is meant a *single dose* of an analgesic such as demerol or seconal given at any time and/or nitrous oxide with contractions at the end of the second stage. *These mothers are fully conscious at delivery.*

3. Those labors in which the mothers appear to receive some benefit from indoctrination but who need a deeper and more prolonged anesthesia are classified as *fair*.

4. Those labors in which the mothers seem to receive no benefit from these techniques, who experience a great deal of pain throughout labor, and in whom the usual amount of analgesia and anesthesia are used, are classified as *poor*.

We also classify the mother's reaction to labor and, in almost all cases where the mother's own appraisal of her experience is at variance with that of the attendants, it has been in the direction of the more successful group.

It is obvious that this classification is arbitrary. Both the "excellent" and "good" group may be said to be successful. This allowance should be made, for the idea that the use of a minimum amount of analgesia and anesthesia constitutes failure must be eliminated. Actually, one can say that exposing patients to the natural childbirth techniques is of definite value in all cases but the "poor" group.

We have compiled various other data and compared such factors as age, physical condition, mental attitude, amount of indoctrination, relaxation, weight of baby, and length of various stages of labor in these patients. As yet the figures show no significant correlation to the techniques, and no positive conclusions can be reached from them. For example, we have not been able to show as yet that the average total length of labor is shortened, nor have we discovered that any single factor will explain success or failure in any individual patient. It seems impossible to predict accurately in any given patient on the basis of any one given characteristic whether or not she will be in the successful group. Our results may be seen in Tables I, II, and III.

From the study of those who have had a poor result, we feel justified in saying that there is a small group of women who cannot achieve natural childbirth. Part of this group is made up of women whom Dr. Read calls unteachable; unteachable because of a lowered intelligence, and are therefore uninterested, or they possess the type of personality which resists teaching or new information of any kind. The rest of this "poor" group is composed of women who have a large degree of subconscious anxiety, particularly centered on childbirth. These women accept the teaching fairly well, but their anxiety becomes evident when labor begins.

As stated before, natural childbirth is primarily based on a physician-patient relationship. The doctor, or doctors, attending the patient must believe in the reality of natural childbirth and must be sympathetic to its aims. Doubt or scepticism on the part of the physician will sooner or later communicate itself to the patient and interfere with a satisfactory result. The keystone of the arch of

TABLE I. VOLUNTEER GROUP

	EXCELLENT	GOOD	FAIR	POOR	TOTAL
Primiparas	20	7	2	0	29
Multiparas	12	4	2	1	19
	32	11	4	1	48
	43 (or 89.58%)		5 (or 10.42%)		

TABLE II. SELECTED GROUP

	EXCELLENT	GOOD	FAIR	POOR	TOTAL
Primiparas	24	22	11	7	64
Multiparas	23	14	1	6	44
	47	36	12	13	108
	83 (or 76.85%)		25 (or 23.15%)		

TABLE III. TOTAL

	EXCELLENT	GOOD	FAIR	POOR	TOTAL
Primiparas	44	29	13	7	93
Multiparas	35	18	3	7	63
	79	47	16	14	156
	126 (80.7%)		30 (or 19.3%)		

indoctrination is education. Knowledge replaces ignorance and banishes fear. This is demonstrated by the success of some of our early cases, who had natural childbirth by virtue of their own knowledge of the subject.

Supporting structures are the relaxation techniques and proper attendance during labor. These two are complementary and interdependent. The specific relaxation techniques used are simple and easily taught prenatally. However, in the majority of cases such teaching must be reinforced during labor, when the patient is under stress. This does not mean that it is always necessary for the doctor to spend the entire labor with the patient. We have observed that many patients, usually intelligent, enthusiastic women who have been given a basic minimum amount of prenatal instruction, can go through a labor with little or practically no support. On the other hand, there are some women who without maximum support during labor will become afraid, cease to relax, lose control, and experience pain. We have found that by utilizing especially trained nurses who are adept at teaching relaxation, the physician is free to attend to other duties. If such nurses are not available, the frequent attendance of the physician is a primary requisite. Dr. Blackwell Sawyer, of Toms River, N. J., a pioneer in this country in these methods, emphasizes that the doctor "must be gentle, solicitous, wise, and, above all, he must be present."

In this study we are fortunate in having specially trained nursing personnel available. In addition, the delivery service nurses have been, or are being, trained to carry on these labor techniques.

If a patient is left more or less alone during labor and is expected to endure a process about which she knows nothing and is told nothing, it is not remarkable that she becomes afraid and therefore becomes tense. If the patient is visited frequently by her doctor in whom she has the utmost confidence, who tells her

frankly what is going on, if, in addition, she is attended more or less constantly by an understanding nurse who helps her adapt her relaxation exercises to labor, she is usually able to go through without experiencing any more discomfort than she is quite willing to bear.

If, on admission, the history and physical examination indicate that the patient is having a slow labor, or it appears likely that it will be unduly prolonged, the administration of a sedative will often give the patient a period of rest which will be of great advantage. In all cases we are careful not to institute relaxation techniques until the patient needs them. If, in the first stage, when the cervix is about 4-6 cm. dilated, the patient finds it difficult to relax despite adequate instruction, a small dose of analgesic, such as demerol or a barbituate, may be given, always with the suggestion that it will aid relaxation.

It must be emphasized that the end of the first stage is the critical period in almost all natural labors. We have found that it is important at this time to tell the mother that after she passes this period and proceeds into the second stage she will feel better.

As the cervix reaches full dilatation there may be a transient nausea, hiccoughs, or merely a catch in the breath, as the patient inhales slowly. It is our practice at this time to ask the mother to hold the breath after inspiration and to attempt a slight bearing-down effort. If the cervix is actually fully dilated at this time, the mother will immediately remark that this feels better. If, however, she complains that this hurts, vaginal examination, if done, usually will show that the cervix is not completely dilated and that there is still a cervical lip present, which could not be palpated per rectum. If the patient is a primigravida, we do not encourage maximum effort at this time, rather we try to have the patient conserve her strength for the latter part of the second stage.

In "Childbirth Without Fear," Dr. Read emphasizes that we can expect a completely natural childbirth only in a normal labor, and he includes in his criteria for normal labor the proviso that the baby shall be in a vertex presentation, and in an occipitoanterior position. He further states that in occipitoposterior positions the patients will have a severe backache which will cause them to need or want anesthesia. This latter we have observed to be true.

In our 156 patients, we have delivered thirteen in posterior position and four in breech presentation. Five of the posterior positions had excellent results, seven good, and two were complete failures. Of the breech deliveries, two had an excellent result, one good, and one failed completely.

Two of our posteriors were persistent, and because of this we were forced to intervene. In neither of these cases did the mother ask for relief. Operative delivery was elected when progress ceased. In the few cases in which we have found it necessary to intervene, we have used pudendal block, or saddle block anesthesia, believing that these mothers wish to be conscious at the time of delivery, particularly if they have been enthusiastic about natural childbirth.

In analyzing our failures we have uncovered some interesting findings. In all of the patients classified as poor, there was more than one factor present by which the failure could be explained. The predominant factor has usually been deep-seated anxiety, noted after the labor started. In several the anxiety had been manifest in the past, and some of these patients had been treated or seen by psychiatrists. The second factor is often lack of proper indoctrination; the patient has not attended the classes, or has failed to comprehend the teaching, or has not practiced the recommended exercises.

From this we may conclude that a patient with an undue amount of anxiety and who will not accept indoctrination is a poor candidate for natural childbirth. The intelligent woman, however, even though anxiety is present, will be greatly aided.

The multipara who has had a relatively large number of children and whose intelligence is not of a very high order is usually a poor candidate. In many instances she may have a delivery without undue discomfort without being exposed to indoctrination. In any case, she is hard to evaluate.

In the evaluation of any innovation it is always useful to consider the advantages and disadvantages. Some of the advantages which we have noted are:

1. The majority of labors are spontaneous. Authorities are in universal agreement that obstetric complications, such as frank sepsis, maternal morbidity, hemorrhage, damage to maternal soft parts, fetal morbidity or mortality, especially fetal cerebral damage, have their lowest incidence in spontaneous deliveries and a rising incidence in operative deliveries, in direct proportion to the severity of the operation.

2. The risks attendant on the use of anesthesia are avoided. There is no anesthetic for obstetric use which is 100 per cent safe for mother and baby and which will not have some effect on labor.

3. Another advantage in natural childbirth which, although it has never received much attention, is very real; namely, the psychological advantage. No one who has seen a natural childbirth can doubt that there is established an immediate and close bond between the mother and her baby. This bond, in the opinion of those psychiatrists who have observed it, should and does provide for a mother-child relationship which can have a deep and lasting effect on their mutual adjustment in the distant, as well as the near, future. Many of our natural childbirth patients go from the delivery room to the rooming-in unit, which is organized to promote and study this relationship. The foundations of mental health in the adult are laid in infancy and childhood, and, since infancy begins at birth, we believe that it is reasonable to suppose that, if childbirth is a happy and satisfying experience, the mother-child relationship will have a sound foundation. That it can be a happy and satisfying experience is irrefutable when the mother's reaction is observed. Many multiparas have told us that natural childbirth was far superior to a previous delivery during which they were "knocked out" and didn't know that they had had a baby until the following day. Several have expressed their feeling of closeness to a baby which they felt they had had themselves in contrast to another which had been delivered while they were unconscious.

For purposes of analysis we interview each mother post partum on her reactions to labor. One of the questions we ask is, "Do you want to have your next baby this same way?" We feel that their response is most significant. We have 148 answers to this question:

One hundred twenty-five patients gave an unqualified—yes.

Seven patients gave a qualified—yes—saying that they would if they felt the doctor was sympathetic enough to give them support.

Nine patients gave an unqualified—no. These were all cases who had failed. Seven said they didn't know. Surprisingly enough, of the 125 who answered "yes" to this question, ten had had only fair results, and three had failed completely.

What of the disadvantages?

The usual charge leveled against natural childbirth is that it is unduly time consuming, especially for a private practitioner. We believe that if an additional five minutes were added to each prenatal visit for the purpose of instruction, it would be sufficient for indoctrination purposes. When the patient is in labor more attention by the physician is necessary than usually may be given, but this need not be excessive or unduly demanding. If nurses who are trained in natural childbirth techniques can be utilized, the amount of extra time necessary would be minimal for most cases. This we believe to be of great advantage;



especially in hospital practice it may be the beginning of a new and greatly important development in delivery room nursing service.

### **Summary**

In considering our experience we believe that we are justified in saying that our limited series has shown that natural childbirth is a definite entity which can be taught successfully in a teaching ward obstetric service. We believe that natural childbirth techniques offer decided advantages to mother and child, and are psychologically desirable for most women.

## STUDY OF THE THYMUS IN 7,400 CONSECUTIVE NEWBORN INFANTS\*

EUGENE A. CONTI, B.S., M.D., F.A.C.S., AND GEORGE D. PATTON, B.S., M.D., M.S.,  
PITTSBURGH, PA.

*(From the Obstetric, Pediatric, and Radiologic Departments of Pittsburgh Hospital)*

THE thymus problem presents today as it has for many decades, a challenge to the physician. Many thoughtful investigators believe that definition and clarification of the physiology of this gland must precede any stable and scientifically sound solution. Controversy has been the keynote of thymus discussion since 1889.

At present there seem to be a few points upon which there is agreement.

1. A competent radiologist experienced in thymus interpretation will usually be able to determine whether the gland is enlarged.<sup>1-3</sup>
2. Many obstetricians and pediatricians believe that respiratory symptoms in the presence of thymus enlargement justify therapeutic radiation.<sup>2, 3, 5, 6</sup>
3. In the majority of cases where no other pathology is demonstrable the respiratory symptoms will improve with the rapid thymus atrophy which follows roentgen therapy.<sup>4-6</sup>
4. There has been no positive proof adduced that sudden death in infants can be due to tracheal compression or bilateral recurrent laryngeal nerve paralysis from enlarged thymus. However, many reliable authorities attest to this possibility and submit autopsy proof of cases which showed no postmortem findings except the presence of an enlarged thymus gland.<sup>5</sup>
5. The general public is thymus conscious and has what is possibly unjustified confidence in the efficacy of roentgen diagnosis and treatment.

The obstetrician has a joint interest with the pediatrician in a solution of this problem because in the early postnatal life of their children parents expect the obstetrician to take whatever measures may be available to forestall future catastrophe. Many obstetricians have delivered babies who were discharged from the hospital in apparent good health and at a later date suddenly died from what was diagnosed as thymus compression. After several such experiences in April, 1938, we began a routine roentgen examination of each newborn infant in an endeavor to prevent such episodes. Over the intervening years we have attempted, in the light of further experience, to modify our technique as seemed conducive toward better results. The material which follows is a presentation of our results from Jan. 1, 1937, to May 1, 1946, comprising a total of 7,391 surviving full-term infants which were delivered at our hospital.

The data were obtained from two sources: first, from the individual infant's chart; second, from a questionnaire addressed to the parents of each child. More detailed information was obtained by telephone contact with all parents who reported thymus enlargement in their children.

\*Presented at a joint meeting of the Obstetrical, Gynecological and Pediatric Societies of Pittsburgh, Feb. 3, 1947.

# Questionnaire

Dear Friend:

The efficiency of routine x-ray examination of the thymus gland in newborn infants is being checked by conducting a survey of results. Its success depends entirely on your cooperation.

Will you kindly answer the following questions, place this letter in the enclosed envelope, and mail at your earliest convenience.

1. Is your child which was born ----- well now? -----  
(date)
  2. Did the child ever have crowing cry, difficulty in breathing or swallowing? -----
  3. Did the doctor ever say the child had trouble with the thymus gland? -----
- If the answer to Question 2 or 3 is "yes," please explain.

Group A comprises 728 surviving full-term babies discharged from the hospital between January, 1937, and April, 1938. We have designated this a control series. No roentgenograms were made from these children. The results are illustrated in Table I.

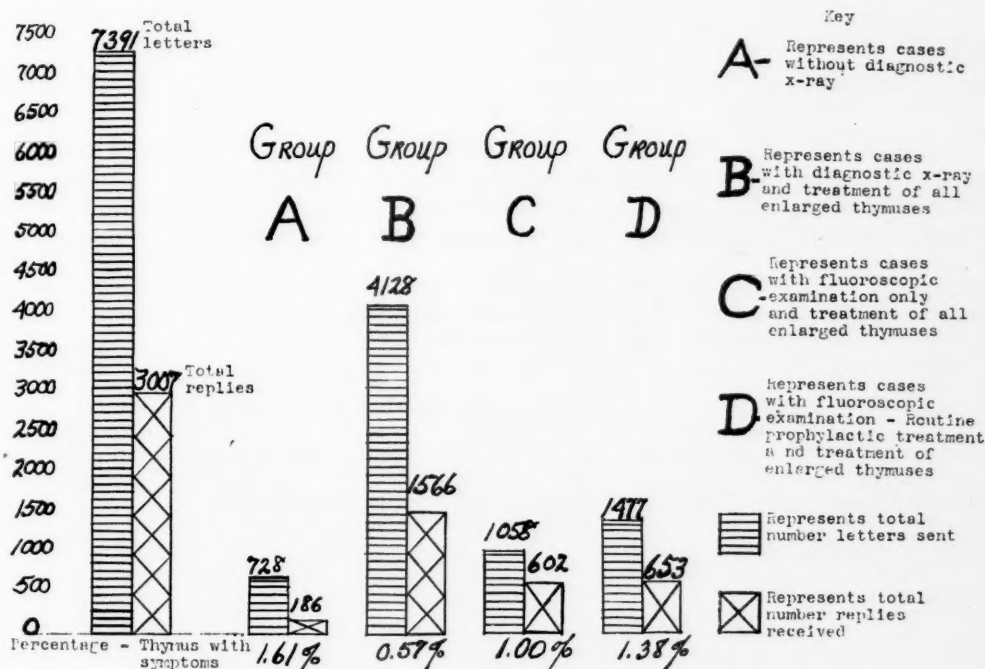


Fig. 1.—Survey, thymus gland, 1937 to 1946.

TABLE I. GROUP A. CONTROL SERIES. NO ROENTGEN EXAMINATION OF THYMUS GLAND

TOTAL INFANTS	REPLIES FROM QUESTIONNAIRE	SYMPTOMS WITH THYMUS ENLARGEMENT	ROENTGEN THERAPY TO THYMUS AT BIRTH	DEATHS DUE TO THYMUS
728	186	3 (1.61%)	0	0

We have designated the cases in Table II as thymus cases because they presented symptoms which suggested respiratory obstruction in the presence of thymus enlargement demonstrable by roentgen examination and in the absence

of any other apparent cause for these symptoms, except in Case 3 where they might be attributed to cretinism. All cases showed improvement or recovery after roentgen therapy.

TABLE II. ANALYSIS OF THREE CASES WITH SYMPTOMS AND ENLARGEMENT OF THYMUS FROM GROUP A

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULTS
1. 3 months	Mild dyspnea	Enlarged roentgen shadow	Roentgen	Recovery
2. 7 months	"Fits of strangulation"	Enlarged roentgen shadow	Roentgen	Recovery
3. 6 weeks	Dyspnea, cough	Enlarged roentgen shadow, cretinism	Roentgen	Improvement

TABLE II A. ANALYSIS OF THREE CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP A

SYMPTOMS	DIAGNOSIS	THERAPY	RESULT
1. Dyspnea	Enlarged adenoids	Adenoidectomy	Improvement
2. Dysphagia	Bronchitis	Bronchoscopy	Death
3. Dyspnea, grunting	Enlarged tonsils	T & A	Recovery

The above table contrasts cases with similar symptoms satisfactorily explained by other causes. Corrective measures were directed to the cause. We were unable to define exactly the condition in Case 2, but conversation with the parents seemed to establish it as some acute infectious bronchial condition.

TABLE III. GROUP B. ROENTGEN FILM MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUSES IN THREE TREATMENTS. APRIL, 1938, TO JUNE, 1943

TOTAL INFANTS	REPLIES FROM QUESTIONNAIRE	SYMPTOMS OF THYMUS ENLARGEMENT	ROENTGEN THERAPY TO THYMUS AT BIRTH	DEATHS DUE TO THYMUS
4,128	1,566	9 (0.57%)	132	2
With enlarged thymus at birth by roentgen examination				
172 (4.1%)	132	0	132	0
With no enlarged thymus at birth				
3,956	1,434	9 (0.63%)	0	2
				Found dead in bed. No autopsy

This group represents our initial effort to prevent future thymus difficulty. There are two figures worthy of note. The incidence of later thymus enlargement in this group is 0.63 per cent compared with 1.61 per cent in the control group, or about one to two and one-half. Of one hundred thirty-two infants which showed thymus hypertrophy and received roentgen therapy, none showed symptoms later. In the two cases of sudden death, both babies were found dead in bed with no history of preceding illness. We do not include them in our thymus cases, although they may have been classified as such in the death certificates. No autopsies were held, so the cause of death remains obscure. These cases both occurred in infants who had shown no thymus enlargement and did not receive therapy.



TABLE IV. ANALYSIS OF NINE CASES WITH SYMPTOMS AND ENLARGEMENT OF THYMUS FROM GROUP B

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULT
1. 4 months	Acute dyspnea	Enlarged roentgen shadow	Roentgen and tracheotomy	Recovery
2. 6 weeks	Crowing cry	Enlarged roentgen shadow	Roentgen	Recovery
3. 6 months	Dyspnea, noisy respiration	Enlarged roentgen shadow	Roentgen	Recovery
4. 2 months	Dyspnea, noisy respiration	Enlarged roentgen shadow	Roentgen	Recovery
5. 10 months	Dyspnea, wheezing	Enlarged roentgen shadow	Roentgen	Recovery
6. 3 weeks	Dyspnea, crowing cry	Enlarged roentgen shadow	Roentgen	Recovery
7. 10 months	Dysphagia, crowing cry	Enlarged roentgen shadow	Roentgen	Recovery
8. 2 weeks	Dysphagia, crowing cry	Enlarged roentgen shadow.	Roentgen tonsillectomy	Recovery
9. 2 weeks	Choking	Enlarged tonsils shadow. Congenital heart	Roentgen	Unrelieved

TABLE IV A. ANALYSIS OF TWENTY-SIX CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP B

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULTS
1.	Crowing cry, dyspnea	Asthma	T & A	Improvement
2.	Wheezing	None	Roentgen	Recovery
3.	Dysphagia	Enlarged tonsils	T & A	Recovery
4.	Dyspnea	Enlarged tonsils	T & A	Recovery
5.	Crowing cry, dyspnea	None	None	Death
6.	Crowing cry, dyspnea	Enlarged tonsils and adenoids, asthma	T & A	Improvement
7.	Crowing cry, vomiting	None	None	None
8.	Dyspnea, dysphagia	Sore throat, cervical adenitis	Symptomatic	Recovery
9.	Crowing cry, dyspnea, dysphagia	None	None	Recovery
10. 3 weeks	Dysphagia, choking	None	None	Recovery
11.	Noisy breathing	Enlarged tonsils. Negative thymus ray	T & A	Recovery
12.	Crowing cry	None	Symptomatic	Recovery
13.	Dysphagia	None	None	Recovery
14.	Dyspnea	None	None	Unrelieved
15. 13 months	Dysphagia, dyspnea, crowing cry	Tracheal obstruction	Tracheotomy	Recovery
16.	Dyspnea, dysphagia	Enlarged tonsils, adenoids. Negative thymus ray	T & A	Recovery
17.	Dyspnea	Enlarged tonsils, adenoids	T & A	Recovery
18. 2 weeks	Dyspnea, cyanosis	Negative thymus ray	None	Recovery
19.	Crowing cry, cough	Negative thymus ray	None	Recovery
20. 1 year	Dyspnea, dysphagia	Enlarged adenoids	Adenoidectomy	Recovery
21.	Dyspnea	None	None	Recovery
22.	Crowing cry, dyspnea, dysphagia	Enlarged tonsils, adenoids	T & A	Recovery
23. 6 months	Wheezing	Asthma	Symptomatic	Unrelieved
24. 4 months	Dyspnea	Negative thymus ray	Roentgen	Recovery
25. 2 months	Crowing cry	None	None	Recovery
26.	Wheezing	Negative thymus ray	Roentgen	Recovery

Table IV presents an analysis of nine cases which we have designated as thymus cases by the same criteria previously mentioned. Note that in Case 1 the patient required a tracheotomy at Children's Hospital. All of the patients recovered with roentgen therapy.

Table IV A presents twenty-six cases in which causes other than thymus enlargement were demonstrated. In some of these, roentgenograms showed no enlargement. In Case 5 was another unexplained death which we could not classify because of insufficient data. The patient in Case 15 recovered without treatment, and others recovered after specific treatment. This presents a point stressed by those who maintain that respiratory symptoms even with thymus enlargement are not due to the thymus.

In June, 1943, at the suggestion of Dr. John McCullough, who has done nearly all the radiologic work in this series, we decided to substitute fluoroscopy for diagnostic films. This change was made for several reasons:

1. To make films requires additional expert help to maintain the baby in proper position.
2. Film processing is more time consuming.
3. Fluoroscopy enables the examiner to discount the effect of respiration on the thymus shadow.
4. Differentiation of the thymus from the cardiac and great vessel shadow is easier when using the fluoroscope.
5. Changing the baby's position facilitates estimation of thymus depth in the lateral position.

TABLE V. GROUP C. FLUOROSCOPIC EXAMINATION MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUSES IN THREE TREATMENTS

TOTAL INFANTS	REPLIES FROM QUESTIONNAIRE	SYMPTOMS OF THYMUS ENLARGEMENT	ROENTGEN THERAPY TO THYMUS AT BIRTH	DEATHS DUE TO THYMUS
1,058	602	6 (1.00%)	12	1
With enlarged thymus at birth by roentgen examination				
32 (3.02%)	12	0	12	0
With no enlarged thymus at birth				
1,026	590	6 (1.02%)	0	1 (Status thymico lymphaticus and adrenal hemorrhage)

Table V presents the results in this group. The incidence of thymus enlargement was somewhat smaller than where a film was taken (3.02 per cent to 4.1 per cent). However, more babies presented symptoms with thymus enlargement at a later date (1.00 per cent to 0.57 per cent). It is again notable that twelve cases which received therapeutic x-ray for enlargement had revealed no symptoms when the questionnaire was returned. One baby which was negative upon discharge from the hospital died at six weeks after an illness of several hours. The pediatrician in attendance stated that the baby had none of the symptoms which are suggestive of thymus enlargement, but did have petechiae and purpuric areas which suggested meningitis. Autopsy showed thymus enlargement, general lymphoid hyperplasia, and adrenal hemorrhage. The latter factor precluded its classification as a thymus death.

TABLE VI. ANALYSIS OF SIX CASES WITH SYMPTOMS OF ENLARGEMENT OF THYMUS FROM GROUP C

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULTS
1. 3 months	Crowing cry	Enlarged roentgen shadow	Roentgen	Recovery
2. 4 weeks	Dysphagia, crowing cry	Enlarged roentgen shadow	Roentgen	Recovery
3. 2 weeks	Dysphagia	Enlarged roentgen shadow (3 months)	Roentgen	Recovery
4. 6 weeks	Dyspnea, crowing cry	Enlarged roentgen shadow	Roentgen at 7 weeks	Recovery
5. 6 weeks	Dyspnea, cyanosis	Autopsy status thymico lymphaticus and adrenal hemorrhage		Sudden death
6. 2 years	Dyspnea	Enlarged roentgen shadow, congenital heart	Roentgen	Improvement

Table VI is an analysis of six cases from Group C which showed later thymus enlargement with symptoms after a negative roentgenogram in the immediate postnatal period. Case 6 showed a coincidental congenital heart. However, the respiratory symptoms improved after radiation.

TABLE VI A. ANALYSIS OF TEN CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP C

SYMPTOMS	DIAGNOSIS	THERAPY	RESULT
1. Crowing cry,	Croup	Symptomatic	Recovery
2. Dyspnea	Adenoids	Not stated	Recovery
3. Dyspnea	Allergic asthma	Not stated	Improvement
4. Dyspnea	Enlarged tonsils	T & A	Recovery
5. Dysphagia	and adenoids		
6. Dyspnea, dysphagia	Enlarged tonsils and cervical glands	None	Unrelieved
7. Dyspnea	Enlarged tonsils	None	Unrelieved
8. Crowing cry, dyspnea	Asthma	None	Recovery
9. Dyspnea	Atelectasis	None	Recovery
10. Dyspnea, dysphagia	Tonsillitis	Symptomatic	Improvement
	None	None	Unrelieved

Table VI A presents ten cases from Group C with symptoms apparently due to other causes than thymus hypertrophy. Case 10 was placed in this group despite the absence of a diagnosis, since we were unable to contact the people for more specific information.

In September, 1944, we noted that thymus enlargement with symptoms occurred in babies whose roentgenograms at birth were negative and never in infants whose positive roentgenograms were succeeded by treatment. We decided that our results might be improved by continuing to give a therapeutic dose (450 roentgen units) to thymuses which were enlarged, and by administering a smaller dose (75 to 150 roentgen units) prophylactically to the thymuses that were considered normal.

Table VII presents our results in this Group D.

We knew even before this survey was made that we were hearing of more infants with obstructive respiratory symptoms than had previously been the case. We were so convinced of this that we reverted to our former procedure

of diagnostic fluoroscopy with therapeutic radiation to enlarged thymuses only, beginning June 1, 1946. In addition, a film was taken of the hypertrophied thymuses for comparison, should later examination be necessary, and also for medicolegal purposes.

TABLE VII. GROUP D. FLUOROSCOPIC EXAMINATION MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUS IN THREE TREATMENTS. PROPHYLACTIC THERAPY OF 75 TO 150 ROENTGEN UNITS GIVEN OVER ALL OTHER THYMUSES

TOTAL INFANTS	REPLIES FROM QUESTIONNAIRE	SYMPTOMS OF THYMUS ENLARGEMENT	ROENTGEN THERAPY TO THYMUS AT BIRTH	DEATHS DUE TO THYMUS
1,477	653	9 (1.38%)	653	2
With enlarged thymus at birth by roentgen examination				
33	11	0	11	1 Dyspnea 2 hours. Death. No autopsy
With no enlarged thymus at birth				
1,444	642	9 (1.40%)	642	1 Sudden death— 3 weeks. Diagnosed thymus. No autopsy

Table VII reveals a sharp increase in incidence of symptoms with thymus enlargement over that found where enlarged thymuses received a therapeutic radiation and the normal ones were untreated (1.40 per cent to 1.02 per cent or 0.63 per cent). The incidence approached that where no diagnostic or therapeutic efforts were made (1.61 per cent). This procedure would more accurately be called provocative. The dosage was reduced from 150 to 75 roentgen units when a few infants showed bronzing of the skin of the exposed area.

TABLE VIII

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULT
1. 3 weeks	Dyspnea, dysphagia, harsh cough, wheezing	Enlarged roentgen shadow	Roentgen	Recovery
2. 4 weeks	Cough, noisy breathing	Enlarged roentgen shadow (9 months)	Roentgen	Recovery
3. 3 weeks	Dyspnea	Enlarged roentgen shadow	Roentgen	Recovery
4. 3 weeks	Noisy breathing	Enlarged roentgen shadow (2½ months)	Roentgen	Recovery
5. 1 month	Dyspnea (required oxygen)	Enlarged roentgen shadow	Roentgen	Recovery
6. 3 weeks	Crowing cry, dyspnea 6 months	Enlarged roentgen shadow	Radium	Recovery
7. 7 months	Choking spells	Not confirmed	None	Relieved
8. 2 months	Dyspnea, crowing cry	Enlarged roentgen shadow	Roentgen	Symptoms relieved but recurred at 8 months
9. 2 months	Noisy breathing	Enlarged roentgen shadow	Roentgen and radium	Recovery



Table VIII is our analysis of cases showing later symptoms. It is interesting to note that in Case 2 the patient had symptoms from the fourth week, showed enlargement by roentgenogram at nine months, and recovered after treatment. Case 7 was not confirmed by roentgen examination and we were unable to interview the people. In Case 8 the patient had a recurrence of symptoms eight months after treatment. In one, Case 6, the patient was treated by radium, and in another, Case 9, by x-ray-radium combination.

TABLE VIII A. ANALYSIS OF NINETEEN CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP D

AGE AT ONSET	SYMPTOMS	DIAGNOSIS	THERAPY	RESULT
1.	Dysphagia	Enlarged thymus	None	Recovery
2.	Dyspnea, crowing cry	Negative thymus ray	None	Recovery
3.	Dyspnea	None	None	Unrelieved
4.	Dysphagia	None	None	Unrelieved
5.	Noisy night breathing	None	None	Unrelieved
6.	Occasional cyanosis	None	None	Recovery
7.	Dyspnea	Acute bronchitis	Symptomatic	Recovery
8.	Dyspnea	Acute bronchitis	Symptomatic	Recovery
9.	Crowing cry, dyspnea	None	None	Unrelieved
10.	Noisy breathing	None	None	Recovery
11. 2 months	Dyspnea	None	None	Recovery
12. 7 months	Dyspnea	Pertussis; negative thymus ray	Symptomatic	Recovery
13.	Dyspnea, dysphagia	Bronchitis	Symptomatic	Recovery
14.	Choking	None	None	Recovery
15.	Crowing cry	Negative thymus ray	None	Recovery
16. 6 months	Dyspnea	Negative thymus ray	None	Recovery
17.	Dyspnea	Asthmatic bronchitis	Symptomatic	Recovery
18.	Dyspnea, crowing cry	None	None	Recovery
19.	Noisy breathing	None	None	Recovery

Table VIII A analyzes nineteen cases with symptoms and no thymus enlargement from Group D. In Case 1 the patient was stated to have enlargement by a notoriously unreliable individual, with a portable x-ray machine, who did not advise treatment, and the baby recovered uneventfully. Several others had negative roentgenograms. Some had definite other causes for their respiratory embarrassment, and the remainder were undiagnosed, untreated, and are no worse or are recovering (Fig. 1).

Fig. 1 is a summary of the results of our survey to date.

### Discussion

1. We are unable to shed any light on the pediatricians' problem in appraising the part that the thymus plays in sudden death in infants. The incidence of this catastrophe in newborns was not reduced by our efforts to forestall it by routine neonatal roentgenograms. Our analyses of the five sudden deaths failed to elicit any proof that they were due to thymus compression. Only one occurred in our hospital, and the autopsy showed purpuric spots and adrenal hemorrhage in addition to thymus enlargement. The pediatrician did not believe the symptoms could be ascribed to the latter condition. The other four cases were glibly diagnosed as thymus deaths by a physician or coroner without autopsy.

2. All of the respiratory symptoms with thymus enlargement reported in the questionnaire groups B, C, and D were from children who had normal thymus roentgenograms in the neonatal period.

3. Groups B and C in which the infants with enlarged thymus shadows received roentgen therapy showed a lower incidence of respiratory symptoms associated with enlarged thymus later. Although the percentage incidence is impressive, a change of only one case in these small groups of nine and six cases would change the picture completely.

4. In group D the incidence of later thymus enlargement with symptoms was higher than in groups B and C. This may indicate that minimal doses of roentgen rays to normal thymuses in the neonatal period are provocative and their use is unwise.

5. Many infants with respiratory symptoms had roentgenograms made of the thymus. Irradiation therapy was given to those in whom an enlarged thymus shadow was seen. Most of these improved. Some infants with the same symptoms and negative roentgenograms improved without therapy; others retain their symptoms.

6. Diagnostic roentgenograms offer some reassurance to parents who are thymus conscious. This is not an undesirable effect. The alleviation of anxiety is a commendable medical achievement.

### Conclusions

1. Negative diagnostic thymus roentgenograms in the neonatal period do not preclude the possibility of enlargement with symptoms at a later date.

2. Infants exhibiting symptoms commonly attributed to thymus enlargement should have roentgenograms. If the thymus shadow is enlarged, roentgen therapy is indicated.

3. In many cases respiratory symptoms occur in the absence of an enlarged thymus shadow. If a specific etiological factor is found and treated the results are generally good. If no cause is found and no treatment given, the results are also generally good.

4. The obstetrician or pediatrician should accede to the wishes of parents who want neonatal roentgenograms of their children. It might even be wise to administer therapeutic dosage over the thymus. Whatever assurance is gained by this apparently harmless and perhaps beneficial procedure will aid in alleviating an anxiety which occasionally becomes a thymus phobia.

5. Neonatal roentgenograms have not aided us in forestalling sudden death in young infants. The benefits to be gained by preventing later enlargement with respiratory symptoms in the 5 per cent who show neonatal thymus enlargement does not justify their use as a routine procedure. Patients in these cases can apparently be adequately and safely treated after the onset of their symptoms.

### References

1. Watson, W. W.: *Arch. Otolaryng.* 4: 495, 1926.
2. Pancoast, Henry K.: *Proceedings Inter-State Post Graduate Medical Assembly of North America* 4: 206, 1929.
3. Pancoast, Henry K.: *Am. J. M. Sc.* 180: 745, 1930.
4. Jackson, Chevalier, and Bowman, James E.: *Am. J. Dis. Child.* 54: 1426, 1937.
5. Leaton, Robert E.: *Texas Rep. Biol. & Med.* 4: 311, 1946.
6. Dann, Daniel S.: *J. Missouri M. A.* 43: 445, 1946.

## AMENORRHEA AND OLIGOMENORRHEA, ETIOLOGY AND TREATMENT

WILLIAM BICKERS, M.D., RICHMOND, VA.

WHEN menstruation fails to occur by the seventeenth year of life the condition may be defined as primary amenorrhea. Menstruation having once occurred, followed by cessation for a period of three months, may be defined as secondary amenorrhea. Oligomenorrhea is a convenient term for designating the long-interval type of menstrual cycle, in which the cycle is prolonged from forty days to three months. Menses occurring in a cycle of 24 to 39 days may be considered within the physiologic range. Functional alterations only are under consideration here and cessation or absence of menses due to the menopause, anatomic defects, pregnancy, castration, hysterectomy or masculinizing tumor are not considered. Occurrence of regular cyclic menstruation between the ages of 14 and 40 usually implies a normal pituitary-ovarian-endometrial physiology and deviation from it suggests, but does not necessarily imply, some defect in endocrine physiology.

Sex physiology has for its ultimate purpose the procreation of the species. The complex pituitary-ovarian-endometrial system with the many tangential influences, intrinsic and extrinsic, acting upon it, is designed for the purpose of cyclically maturing a potentially fertile ovum and the preparation of the endometrium for its nidation. Until recently we have taught that menstruation in itself served no useful function. Some doubt is cast upon this concept, however, by recently published work which has demonstrated the presence of a highly toxic euglobulin fraction in the menstrual discharge. Clinically, it is well known that delayed menstruation is associated with nervousness, irritability, breast fullness, lower abdominal pain, a syndrome to which has been given the term "menstrual molimina." It is shown in this study that amenorrhea and oligomenorrhea are associated with ovulation failure in a relatively high percentage of patients and endometrial defects other than those associated with ovulation failure are occasionally encountered. Fertility of these patients is impaired and the incidence of spontaneous abortion is approximately three times that observed in cyclically menstruating women. The data to support these statements will be presented in a subsequent report. From this brief résumé, however, it may be assumed that the induction of cyclic menstruation is desirable from a psychological standpoint, necessary for the patient's well-being, and an important adjunct to the treatment of sterility in the female.

### Material

Records from Jan. 1, 1940, through Aug. 31, 1947, have been reviewed. There were 4,251 patients who consulted or were referred to an office in which the practice is limited to gynecology and obstetrics. Of this group, 1,001 were known or subsequently proved to be pregnant. There were 417 patients either

under the age of 17 or past the age of 39 years and these were eliminated from this study for obvious reasons. This left 2,833 records on patients from 17 through 39 years who are known to have been nongravid and who consulted the office for various gynecic complaints. In this group, there were 1,291 patients who gave as their chief complaint some disturbance in amount, duration, or periodicity of the menses. In this group, 416 patients complained of amenorrhea or oligomenorrhea. Of this selected group, 78 were shown at the initial visit or subsequently proved to have some demonstrable organic lesion to explain the absence, delay, or cessation of their menstruation. This left a group of 338 patients who could be classified as functional amenorrhea or functional oligomenorrhea. It is presumed that some of these patients had organic disease which was neither diagnosed at the initial visit nor diagnosed subsequently. There were 296 patients with amenorrhea or oligomenorrhea on whom the records are complete and the results reported here are based on a study of this group. Others could not be followed or refused treatment.

On the basis of the above statistics, it can be said approximately 45 per cent of the patients from 17 to 40 years of age consulting a gynecologist in private practice have as their chief complaint some disturbance in menstruation. In about 12 per cent, the chief complaint is amenorrhea or oligomenorrhea of a functional nature, using the criteria for diagnosis which this observer deems adequate.

### Primary Amenorrhea

Forty-seven patients with primary amenorrhea varied in age from 17 to 34 years. When the menses failed to appear by the seventeenth birthday, the patient was classified as having primary amenorrhea. Endometrial biopsies were obtained on 18 of these patients and a proliferative phase endometrium was found in all. The tissue varied from the very thin atrophic type, found in three patients, to a marked cystic hyperplasia which was demonstrated in two patients. One of the latter group was the oldest patient in the series, namely, 34 years of age. All other biopsies showed the usual persistent proliferative phase with straight tubular glands, compact stroma, and a minimal degree of vascularization.

The secondary sex characteristics were poorly developed in four patients. One of these showed practically no mammary development, a minimal amount of hirsutism and complete absence of the usual female fat distribution. The majority of these patients, however, showed relatively normal development of the secondary sex characteristics and on gross examination could not have been differentiated from normally menstruating women.

### Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 17 patients in this group seen from Jan. 1, 1940, through Dec. 31, 1944, who were treated with cyclic stilbestrol-progesterone therapy. The earlier cases received 5 mg. stilbestrol daily for twenty days and 5 mg. progesterone daily for the last five days of stilbestrol therapy. Treatment was then discontinued until the onset of the first induced bleeding episode. The twenty-day treatment with stilbestrol-progesterone was then resumed according to the same schedule, the treatment being started on the fifth day of the induced cycle. Stilbestrol was administered in a 5-mg. dose daily from the fifth through the twenty-fifth day of the cycle; progesterone in 5-mg. dose was given from the twentieth through the twenty-fifth day of the cycle. Uterine bleeding occurred in eight patients within six days after completing the first twenty-day treatment course. In all patients who menstruated after the first cycle of treatment, the bleeding recurred during the three consecutive cycles of treatment. Cyclic menstruation continued in only 5 patients



for as long as three months following cessation of treatment and only two of these menstruated from a secretory-phase endometrium, indicating that ovulation had followed as a result of, or concomitant with, the treatment in only two patients out of seventeen. The others in the group lapsed either into a completely amenorrheic phase or continued to have long-interval uterine bleeding from a proliferative phase endometrium. Cyclic bleeding was established in 29 per cent of the group for a period of three months after completing treatment, ovulation salvage was 12 per cent.

(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, there were 13 patients with primary amenorrhea who were treated on cyclic sterol schedule using 0.3 mg. ethinyl estradiol daily from the fifth through the twenty-fifth day of the cycle and 5.0 mg. progesterone on the twentieth through the twenty-fifth day of the cycle. Endometrial biopsies were done on eight of these patients; all had a persistent proliferative phase. It was observed that these patients tolerated the treatment with less nausea and fewer side reactions than the stilbestrol-treated group. The incidence of estrogen-progesterone withdrawal following the first twenty-day course of treatment was better than that observed in the stilbestrol group; ten patients showed evidence of bleeding within five days after completing the first twenty-day period. Treatment with ethinyl-estradiol-progesterone was continued for 3 consecutive treatment periods in the ten patients who menstruated following the first course of treatment. In one patient, a second course was instituted even though the first was not followed by bleeding, but in this case the second course of treatment did not accomplish that which the first had failed to do. In all patients who menstruated following the first course, cyclic menstruation continued during the three months of treatment. After completing three months of ethinyl-estradiol-progesterone therapy, seven patients continued to have cyclic menstruation for at least three months. Of this group, five patients menstruated from a secretory phase endometrium; three lapsed into an amenorrheic phase or continued to menstruate at long and irregular intervals from a proliferative phase endometrium. Cyclic bleeding was established in 54 per cent for a period of at least three months after completing treatment, and the ovulation salvage was 39 per cent.

(c) *Prometron*.—During the year 1947, 17 patients suffering from primary amenorrhea were treated by the intramuscular injection of Prometron, a mixture containing 2.5 mg. of estradiol benzoate and 12.5 mg. of progesterone in 1 c.c. of sesame oil. This was administered daily for two days immediately after the diagnosis had been established. Patients in this group varied in age from 18 to 32 years. Endometrial biopsy was obtained on 9 of these patients before treatment and all were found to have a persistent proliferative phase. All patients were seen one week after completing the two-day treatment course and in only one did uterine bleeding occur; this was on the sixth day after completion of treatment. Four of these patients were subjected to a second course of treatment and in none did uterine bleeding appear within a week after completing the course. The one patient who did have uterine bleeding after the initial treatment was given another two-day course on the twenty-fifth and twenty-sixth day of the induced bleeding cycle and menstruation was again induced. It may be assumed that two days of treatment with Prometron in a group of patients with primary amenorrhea is followed by no cyclic bleeding and no ovulation salvage.

### Secondary Amenorrhea

Patients who had formerly menstruated, but in whom a period of amenorrhea for three months or more had supervened were so classified. There were 94 patients in this group whose ages varied from 22 to 37 years. The shortest period of amenorrhea was three months and the longest interval seventy-three

months. There were seven patients in whom the amenorrhea occurred following pregnancy and in one case there was a severe hemorrhage at delivery with signs of pituitary failure after delivery. Three cases developed an amenorrhea following a severe febrile illness, in others no demonstrable cause was apparent. Biopsies are available for study on seventy-two patients in this group, the number varying from one to six on each patient. Prior to treatment, sixty-five patients had a persistent proliferative phase and seven showed a persistent secretory phase upon repeated biopsies. Those patients having a proliferative phase varied from moderate atrophy in eleven cases to cystic hyperplasia in twelve cases. In the group of patients with a secretory phase endometrium, there was a history of normal fertility in four patients, while in the much larger group with proliferative phase endometria there was a history of pregnancy in only nine patients. It is presumed that secondary amenorrhea associated with a secretory phase endometrium is the result of persistent corpus luteum activity. When the corpus luteum fails to undergo atresia there is no estrogen-progesterone withdrawal and menstruation fails to occur.

The secondary sex characteristics were well developed in all patients in this group. There was a marked hirsutism in two cases, but the family history in both supported the conviction that this was on a genetic basis.

### Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 20 patients in this group seen from 1941 through 1945 who were treated with some form of cyclic stilbestrol-progesterone therapy. The estrogen was administered from the fifth through the twenty-fifth day of the cycle in varying doses and progesterone was administered on various dose schedules between the fifteenth and twenty-fifth days of the cycle. Although the treatment schedules varied somewhat in the type and dose of progesterone used, the essentials of the cyclic sterol treatment were preserved in all during this period. It was observed that uterine bleeding occurred in fourteen patients within six days after completing the first twenty-day treatment course and all of these were in that group which had a proliferative phase endometrium at the onset of the treatment. In no patient with a secretory phase endometrium (four patients) did uterine bleeding follow treatment. In the fourteen patients who bled after the first course of treatment, the cyclic treatment was carried on for three consecutive months, during which time cyclic uterine bleeding was established in all fourteen. A follow-up 3 months after treatment revealed that ten patients (50 per cent) continued to menstruate on a cycle of 26 to 38 days after completing three months of treatment. The other 50 per cent lapsed into their former amenorrheic state. In the group that continued to have cyclic bleeding for three months (ten patients) after discontinuing treatment, there were four who, by biopsy, were shown to be menstruating from a secretory phase endometrium. This gave an ovulation salvage of 20 per cent for the entire group treated with cyclic stilbestrol-progesterone therapy.

(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, the treatment schedule was standardized, using 0.3 mg. ethinyl-estradiol daily from the fifth through the twenty-fifth day of the cycle and 5 mg. progesterone daily from the twentieth through the twenty-fifth day of the cycle. There were twenty-six patients so treated. Of this group, twenty had a proliferative phase endometrium and six had a secretory phase endometrium before treatment. Cyclic uterine bleeding was established in twenty patients while under treatment, and all of these were in the group having a proliferative phase endometrium before treatment. In only two patients with a secretory phase endometrium did uterine bleeding occur while under treatment and in these the

bleeding had no relation to the schedule of treatment. Cyclic uterine bleeding persisted for a period of at least three months in 61 per cent (sixteen patients) after treatment was discontinued. A study of the endometriums from these patients some months after concluding the three-month treatment schedule revealed that 31 per cent (eight patients) were menstruating cyclically from a secretory phase endometrium as compared with a 13 per cent ovulation salvage in the group treated with stilbestrol.

(c) *Prometron Therapy*.—During the months from September, 1946, through August, 1947, 48 patients with secondary amenorrhea have been treated with Prometron, 1 c.c. daily for two days. Twenty-one patients had uterine bleeding within six days after the second injection and each of these patients had a proliferative phase endometrium prior to the onset of the treatment. In none of the eight patients with a secretory phase endometrium before treatment did bleeding occur. Each of the successfully treated patients received another two-day course of treatment on the twenty-fifth and twenty-sixth days of the induced cycle and uterine bleeding occurred in all. The treatment was repeated for a third consecutive month. Six patients menstruated again without treatment within thirty-five days of the last induced bleeding episode, all the others lapsed into their previous state of secondary amenorrhea. In no case of induced uterine bleeding with Prometron did the patient menstruate from a secretory phase endometrium following treatment. In summary, cyclic bleeding was established in 58 per cent while under treatment, 13 per cent continued to have cyclic bleeding after treatment was completed. There was no ovulation salvage.

In the eight patients of this group who had a secretory phase endometrium before treatment, none had uterine bleeding following the administration of Prometron.

#### Oligomenorrhea

There were 155 patients with oligomenorrhea treated between Jan. 1, 1940, and Aug. 31, 1947. These patients varied in age from 17 to 35 years. Prior to treatment, endometrial biopsies were obtained on 111 of these patients and a proliferative phase was found in 98 and a secretory phase in 13. In the proliferative phase group, there were six with marked hyperplasia and ten who showed atrophy. In twenty-two patients, the long interval menstruation dated from a pregnancy, abortion, or full-term delivery, in thirteen the menstrual difficulty began following a severe febrile illness. Marked obesity was associated in three and extreme emaciation in one.

#### Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 84 patients treated with stilbestrol-progesterone cyclic therapy. The great majority of cases received 5 mg. stilbestrol daily for twenty days and 5 mg. progesterone daily for the last five days of stilbestrol therapy. The others were treated on varying dose schedules, but the essential features of cyclic sterol therapy were preserved in all. There were 218 biopsies on 68 patients in this group, biopsy being taken before and after treatment and at the follow-up examination three months after completing the treatment. Uterine bleeding occurred within six days in 81 per cent (eighteen patients) who had a proliferative phase endometrium at the onset of treatment. No patient with a secretory phase endometrium had bleeding following the twenty-day treatment course. Cyclic bleeding was established in 81 per cent of this group during the three months of treatment. Follow-up examination three months after concluding treatment showed that 68 per cent of the entire group continued to have cyclic menstruation and, of these, 36 per cent bled from a secretory phase endometrium. This provided a presumptive ovulation salvage for the entire group of 36 per cent.



(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, the treatment schedule was standardized, using 0.3 mg. ethinyl-estradiol from the fifth through the twenty-fifth day of the cycle, and 5 mg. progesterone from the twentieth to the twenty-fifth day of the cycle. There were 48 patients so treated. Of this group, forty had a proliferative phase endometrium and eight had a secretory phase endometrium before treatment. Cyclic uterine bleeding was established in 75 per cent (thirty-six patients) while under treatment and all of these were in the group having a proliferative phase endometrium. Cyclic uterine bleeding persisted for a period of at least three months in 67 per cent of these patients after treatment was completed. The study of the endometrium at follow-up examination revealed that 58 per cent menstruated from a secretory phase endometrium, as compared with 35 per cent in the group treated with stilbestrol-progesterone, a presumptive ovulation salvage of 58 per cent in the ethinyl-estradiol group, as compared with 35 per cent in the stilbestrol group.

(c) *Prometron Therapy*.—During the months from September, 1946, through August, 1947, twenty-three patients with oligomenorrhea have been treated with 1 c.c. Prometron daily for two days. There were eighteen patients with a proliferative phase endometrium and five with a secretory phase. Fourteen patients (60 per cent) had uterine bleeding within six days after the second injection and all of those in whom uterine bleeding was induced had a proliferative phase endometrium before treatment. Cyclic Prometron therapy was begun in these patients, giving them the injection on the twenty-fourth and twenty-fifth days of the induced cycle; such treatment was given for three consecutive months. During treatment, 43 per cent of the total number in this group had cyclic uterine bleeding. Only 6 per cent continued to menstruate cyclically for three months after treatment was discontinued, however, and none of these menstruated from a secretory phase endometrium. It is apparent that Prometron was capable of inducing menstruation in 43 per cent of patients in the oligomenorrhea group while under treatment but only 6 per cent of the group were permanently benefited by treatment.

### Summary

Approximately 45 per cent of all patients between 17 and 40 years of age consulting a gynecologist in private practice have as their chief complaint a disturbance in the amount, duration, or periodicity of the menstrual cycle. Amenorrhea or oligomenorrhea of a functional nature occurs in 12 per cent of all patients. Primary amenorrhea was invariably associated with a proliferative phase endometrium in every patient seen by this investigator. Secondary amenorrhea was associated with a proliferative phase endometrium in 85 per cent of patients and oligomenorrhea was so associated in 79 per cent. Those patients of the secondary amenorrhea and oligomenorrhea groups who had a secretory phase endometrium had a consistently poor response to any therapy directed toward establishing cyclic bleeding.

### Treatment

All patients with amenorrhea or oligomenorrhea were treated by one of the following three treatment schedules:

(a) *Stilbestrol-Progesterone Therapy*.—This consisted of 5 mg. stilbestrol daily for 20 days orally and 5 mg. progesterone on the last five days of stilbestrol therapy. Cyclic treatment of this type was administered for three consecutive months, beginning on the fifth, and ending on the twenty-fifth, day of the cycle.



(b) *Ethinyl-Estradiol-Progesterone Therapy*.—This consisted of 0.3 mg. ethinyl-estradiol daily for twenty days orally and 5 mg. progesterone intramuscularly on the last five days of ethinyl-estradiol administration. Cyclic treatment of this type was carried on for three consecutive months beginning on the fifth, and ending on the twenty-fifth, day of the induced bleeding episodes.

(c) *Prometron Therapy*.—Mixed estradiol benzoate, 2.5 mg., and progesterone, 12.5 mg., in sesame oil was administered intramuscularly daily for two days. The treatment was carried on for three consecutive months, administering the mixed hormones on the twenty-fourth and twenty-fifth days of the induced bleeding episode.

In order to evaluate each type of treatment as regards its ability to induce withdrawal bleeding, establish cyclic bleeding while under treatment, induce cyclic bleeding for a period of three months following treatment, all patients were divided into three groups, viz., primary amenorrhea, secondary amenorrhea, and oligomenorrhea. There were 568 endometrial biopsies taken, as noted in the body of this paper. They were used as a means of classification and diagnosis, as well as to evaluate the effects of treatment, particularly in regard to ovulation salvage. It was observed that all patients with amenorrhea or oligomenorrhea who had secretory phase endometria at the onset of treatment failed to respond to any type of cyclic sterol therapy. It may be assumed that failure to menstruate in these patients is a result of persistent corpus luteum activity and that the endometrium, already under the influence of estrogen-progesterone, does not respond to any additional stimulation. The degree of endometrial atrophy or hypertrophy, as well as her past history, has a definite relationship to the patient's response to treatment. Patients with marked atrophy of the endometrium responded less well than those with normal or hyperplastic tissue. That ovulation failure was usually associated with amenorrhea or oligomenorrhea is supported by the fact that 86 per cent of the patients had a proliferative phase endometrium prior to treatment.

### Conclusions

#### PRIMARY AMENORRHEA.—

*Stilbestrol-Progesterone Therapy*.—Cyclic bleeding was established in 48 per cent of patients while under treatment and persisted in 29 per cent for a period of three months after completing treatment. The ovulation salvage for the entire group was 12 per cent following three months of consecutive treatment.

*Ethinyl-Estradiol-Progesterone Therapy*.—Cyclic bleeding while under treatment was established in 79 per cent and persisted for a period of three months after discontinuing treatment in 54 per cent. The ovulation salvage was 39 per cent after three consecutive months of treatment.

*Prometron Therapy*.—Cyclic bleeding was established while under treatment in 6 per cent and persisted for a period of three months after discontinuing treatment in no patients. There was no ovulation salvage after three consecutive months of treatment.

#### SECONDARY AMENORRHEA.—

*Stilbestrol-Progesterone Therapy*.—Cyclic bleeding was established while under treatment in 70 per cent of patients and continued for a period of three

months after treatment was discontinued in 50 per cent. There was an ovulation salvage of 20 per cent.

*Ethinyl-Estradiol-Progesterone Therapy.*—Cyclic uterine bleeding was established in 79 per cent while under treatment and persisted for a period of three months after treatment was discontinued in 61 per cent. Ovulation salvage was 13 per cent.

*Prometron Therapy.*—Cyclic uterine bleeding was established in 58 per cent while under treatment and 13 per cent continued to have cyclic bleeding three months after treatment was completed. There was no ovulation salvage.

#### OLIGOMENORRHEA.—

*Stilbestrol-Progesterone Therapy.*—Cyclic bleeding was established while under treatment in 81 per cent and persisted for a period of three months after completing treatment in 68 per cent. Ovulation salvage was 36 per cent.

*Ethinyl-Estradiol-Progesterone Therapy.*—Cyclic uterine bleeding was established while under treatment in 86 per cent and persisted for a period of three months in 67 per cent. Ovulation salvage was 68 per cent.

*Prometron.*—Cyclic bleeding was established while under treatment in 43 per cent, but only 6 per cent continued to menstruate cyclically for three months after treatment was discontinued. There was no ovulation salvage.

It may be concluded that the most satisfactory treatment for amenorrhea and oligomenorrhea, judged from the standpoint of ovulation salvage or the establishment of cyclic uterine bleeding, is the three months' cyclic administration of ethinyl-estradiol-progesterone according to the plan described. The most convenient form of therapy, where ovulation salvage is not an objective, is to be found in the daily injection of a mixture of estradiol and progesterone over a period of two days. The latter must be considered only as symptomatic treatment. It cannot be recommended on the basis of known gynecic physiology, for the young woman who is amenorrheic is in need of more than palliative treatment. Her capacity to reproduce is at stake. Nothing less than the best therapy known should be advised and cyclic estrogen-progesterone administration is the best available at present.

#### References

- Anspach, B. M., and Hoffmann, J.: *AM. J. OBST. & GYNEC.* 26: 147-160, 1933.  
Kennedy, F. L.: *Hahneman. Month.* 69: 681-683, 1934.  
Rock, J.: *New England J. Med.* 210: 1303-1310, 1934.  
Zacharin, D.: *M. J. Australia* 2: 471, Sept. 17, 1938.  
Anspach, Brook M.: *Am. J. Surg.* 48: 209, 1942.  
Zondek, B.: *Semane med. españ.* 6: 304, 1943.  
Allen, Willard M.: *South. M. J.* 36: 415-420, 1943.  
Bickers, William: *AM. J. OBST. & GYNEC.* 48: 58-68, 1944.  
Beclere, Claude: *Presse Méd.* 12: 175-177, 1946.  
Freed, S. Charles: *West. J. Surg.* 54: 1-9, 1946.  
Rakoff, A. E.: *AM. J. OBST. & GYNEC.* 51: 480-491, 1946.  
Randall, Lawrence M.: *AM. J. OBST. & GYNEC.* 53: 453-458, 1947.  
Randall, Lawrence M.: *Chicago Med. Soc. Bull.* 49: 603-606, 1947.

Hormone preparations for amenorrhea: *Pharmac. Int.*, p. 48, Nov., 1947.  
Ethinyl-Estradiol and Progesterone supplied by the Schering Corporation.

## OVULATION STUDIES WITH DIRECT CURRENT POTENTIALS\*

HERBERT F. NEWMAN, M.D., NEW YORK, N. Y.

(From the Beth Israel Hospital)

THE literature in the field of bioelectric phenomena has reached considerable proportions, with Lund's recent monograph<sup>1</sup> containing a bibliography of more than fourteen hundred references. This investigation is primarily concerned with some clinical applications of the determination of standing direct current potentials. For consideration of the mechanism whereby electric potentials are generated by living cells, the detailed studies of Osterhout,<sup>2</sup> Lund,<sup>1</sup> and Beutner<sup>3</sup> should be consulted. In general, with suitable instrumentation, a potential difference between the surface of various epithelial structures or even between microscopic areas on the surface of single cells can be detected. Lund and his co-workers<sup>1</sup> have presented a large volume of careful evidence as to the importance of surface potentials in affecting the direction and rate of plant growth. In mammals, measure of potential differences has been used as an index of ovulation,<sup>4</sup> to chart the rate of wound healing,<sup>5, 6</sup> to map denervated areas,<sup>7</sup> in the diagnosis of carcinoma of the cervix,<sup>8</sup> and to indicate tissues with a relatively high probability of becoming malignant.<sup>9</sup>

### Method

The Schorr-Lamport millivoltmeter<sup>10</sup> with a ten megohm input impedance was used. This large input impedance should preclude correction for skin resistance but recent investigations suggest that areas of sympathectomized skin may develop resistances of the order of five megohms. The exploring electrodes were of the type recommended by Burr,<sup>11</sup> consisting of coils of Ag-AgCl<sub>2</sub> sealed in a segment of glass tubing whose open end was obturated by a small sponge. The tube was filled with boiled normal saline solution to avoid bubbles. For skin and mucosal surfaces, the electrodes were held by hand and lightly touched to the test area, avoiding any pressure which would squeeze the sponge excessively and change the electrical conduction of the saline bridge.

### Findings

*Human Skin Potential Patterns.*—It must be emphasized that potential difference (P.D.) is being measured and the location of both electrodes is of importance. In a group of six normal women, potential differences between various areas of skin was determined during the intermenstrual period. The diameter of the electrode contact with the skin was 3 mm.

Table I indicates the range of variation in P.D. between various parts of the skin surface. This may be as high as 40 mv. The skin of distal portions of an extremity tends to be electronegative to that of more proximal portions and that of the anterior surface of the upper extremity is always electronegative to the skin of the posterior surface at the same level. The skin of symmetrical portions of the body revealed relatively small potential differences, less than 10

\*This investigation was enabled by a grant furnished by the Joseph and Helen Yeamans Levy Foundation.

TABLE I. VARIATION IN SKIN POTENTIAL DIFFERENCES IN NORMAL WOMEN

ACTIVE ELECTRODE	INDIFFERENT ELECTRODE	P.D. RANGE (MV.)
1. Anterior surface of arm		
Distal phalanx, index finger	Mid phalanx, index finger	-10 to plus 15
Mid phalanx, index finger	First phalanx, index finger	-15 to -5
First phalanx, index finger	Center, palm	-5 to plus 16
Center, palm	Center, wrist	-25 to 0
Center, wrist	Center, mid forearm	-25 to -5
Center, mid forearm	Center, antecubital fossa	-15 to plus 12
Center, antecubital fossa	Center, mid arm	-8 to 0
Center, mid arm	Tip of acromion	0 to plus 5
Tip of acromion	Sterno-clavicular joint	0 to 0
Distal phalanx, index finger	Distal phalanx, thumb	-10 to 0
Distal phalanx, third finger	Distal phalanx, thumb	-7 to plus 5
Distal phalanx, fourth finger	Distal phalanx, thumb	-5 to plus 3
Distal phalanx, fifth finger	Distal phalanx, thumb	-7 to plus 3
Distal phalanx, index finger	Tip of acromion	-30 to -23
2. Posterior surface of arm		
Distal phalanx, index finger	Mid phalanx, index finger	-18 to plus 2
Mid phalanx, index finger	First phalanx, index finger	-12 to plus 5
First phalanx, index finger	Center, dorsum of hand	-20 to plus 5
Center, dorsum of hand	Center, dorsum of wrist	-10 to plus 4
Center, dorsum of wrist	Center, mid forearm	-13 to plus 2
Center, mid forearm	Tip of olecranon	0 to plus 2
Tip of olecranon	Center, mid arm	-5 to plus 5
Center, mid arm	Tip of acromion	plus 1 to plus 1
Tip of acromion	Tip, seventh cervical spine	-2 to 0
Distal phalanx, index finger	Distal phalanx, thumb	-15 to plus 5
Distal phalanx, third finger	Distal phalanx, thumb	-20 to plus 15
Distal phalanx, fourth finger	Distal phalanx, thumb	-5 to plus 2
Distal phalanx, fifth finger	Distal phalanx, thumb	-5 to 0
Distal phalanx, index finger	Tip, seventh cervical spine	-23 to -20
3. Anterior surface of lower extremity		
Distal phalanx, first toe	Proximal phalanx, first toe	-9 to plus 6
Proximal phalanx, first toe	Center, ankle	-5 to -4
Center, ankle	Center, leg	-15 to -15
Center, leg	Center, patella	-15 to plus 10
Center, patella	Center, mid thigh	-4 to plus 5
Center, mid thigh	Center, inguinal fold	-18 to -5
Medial malleolus	Umbilicus	-19 to -9
Distal phalanx, second toe	Distal phalanx, first toe	-5 to plus 10
Distal phalanx, third toe	Distal phalanx, first toe	plus 3 to plus 18
Distal phalanx, fourth toe	Distal phalanx, first toe	plus 10 to plus 10
Distal phalanx, fifth toe	Distal phalanx, first toe	0 to plus 13
4. Right nipple	Right scapula	-5 to -3
Left nipple	Left scapula	-5 to 0
5. Anterior surface of arm	Posterior surface	-15 to -1
Distal phalanx, index finger		-23 to 0
Middle phalanx, index finger		-20 to -5
Proximal phalanx, index finger		-40 to -3
Mid portion, hand		-15 to 0
Center, wrist		-12 to 0
Center, forearm		-20 to 0
Center, elbow		-4 to 0
Center, mid arm		-3 to plus 9
6. Right side of body to left side of body		
Distal phalanx, index finger		-3 to plus 9
Wrist		-3 to plus 1
Elbow		-2 to plus 6
Patella		-2 to plus 2
Dorsum of ankle		-1 to plus 8
Scapula		-1 to plus 1
Nipple, breast		-1 to plus 1



mv. The size of the area tested is significant, for areas a centimeter or less apart may demonstrate a P.D. of as much as 20 mv. Potential patterns may be relatively unstable, varying in the same patient from minute to minute with a range of variation exceeding 5 mv. The emotional factors affecting P.D. were not explored but it was noticed that the skin wounds which were painful showed higher P.D. than painless ones. In a single case of a nonulcerated, uninflamed epithelioma of the forehead, no P.D. could be secured between the tumor area and the adjacent normal skin.

### Studies in Ovulation

Burr and his co-workers<sup>4, 12, 13, 14</sup> have reported changes in P.D. between vagina and pubis in the rat and rabbit and between cervix and ankle, cervix and symphysis, and between right and left index fingers in the human being which they believe serve as an index of ovulation. The evidence has been more convincing in lower animals than in human beings. In a single rabbit,<sup>15</sup> they found a gradual rise in P.D. between vagina and pubis with superimposed rapid shifts in P.D. which they believed to indicate ovulation with the rapid rises in P.D. accompanying the physical expulsion of each ovum. Rogers<sup>16</sup> secured correlation between cyclic changes in P.D. and vaginal smears in the rat using vaginal and pubic electrodes. This was confirmed by Nicholas and Carmosino<sup>17</sup> who failed to secure significant P.D. changes in immature or pregnant rats. Burr et al.<sup>12</sup> reported a single observation in a human being wherein a sharp rise in P.D. between vagina and pubis was observed fourteen hours before a punctate hemorrhage of a ruptured follicle was discovered at laparotomy. More indirect evidence was furnished by Langman and Burr<sup>13</sup> in human cervix to ankle P.D. studies. They found that the cervix was usually 5 to 25 mv. electropositive to the ankle but that, in nine of fourteen cycles studied, it became electronegative for at least one day of the cycle. Barton in Burr's laboratory presented similar type of evidence<sup>14</sup> in a study of P.D. between right and left index fingers, describing peaks significant of ovulation which were absent in men or in women during the menopause. Snodgrass et al.<sup>18</sup> repeated this work but could not find any difference between the types of tracings secured in normal menstruating women and those from surgical castrates or pregnant women. Barton could not correlate index finger P.D. and cyclical body temperatures. She also found that "significant peaks" in index finger P.D.'s occurred in every decile of the menstrual cycle including the menses and that many single cycles showed multiple peaks. Langman and Burr's cervix to ankle P.D. peaks occurred on the 3rd, 6th, 7th, 8th, 13th, 14th, 18th, and 21st days of the cycles.

Using Burr and Barton's index finger technique, wherein the P.D. is measured between the right and left index fingers immersed in beakers of saline connected by saline bridges to the electrodes, six normal nulliparous laboratory workers with regular menstrual cycles were tested daily throughout at least one full cycle. Burr's finding that the pressure of the ball of a finger against the wall of the beaker may modify the P.D. was repeatedly confirmed. This may be attributed to the fact that pressure causes a portion of the digit to lose electrical contact with the saline and the resultant P.D. reflects that of the skin surface still immersed in the fluid. As the dorsum of the finger is electropositive to the volar surface, the P.D. shift on pressure is to the positive side. With a surface area as large as a digit, the resultant P.D. reflects a series-parallel type of relation between multiple areas of widely varying P.D. and the digital P.D. changes may be due to changes in electrical potential of the skin of the entire digit or of only small areas of the digit.

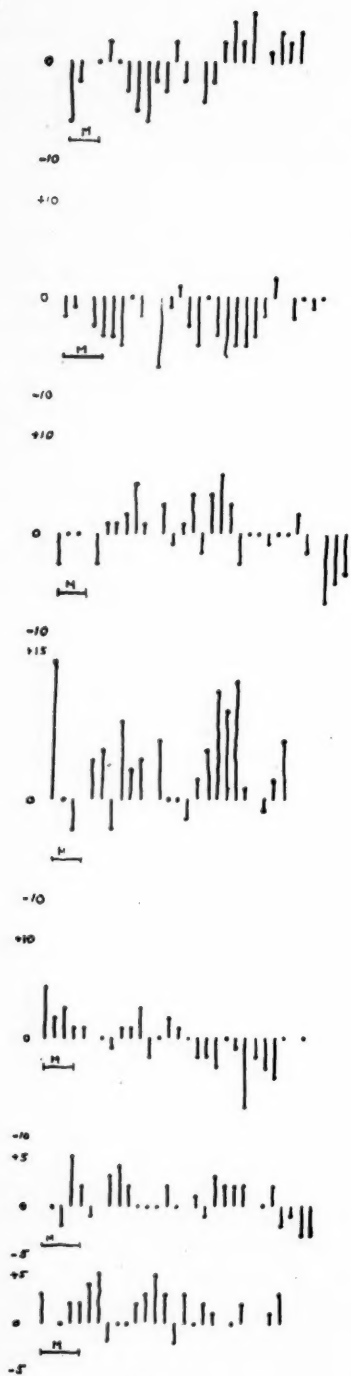


Fig. 1.

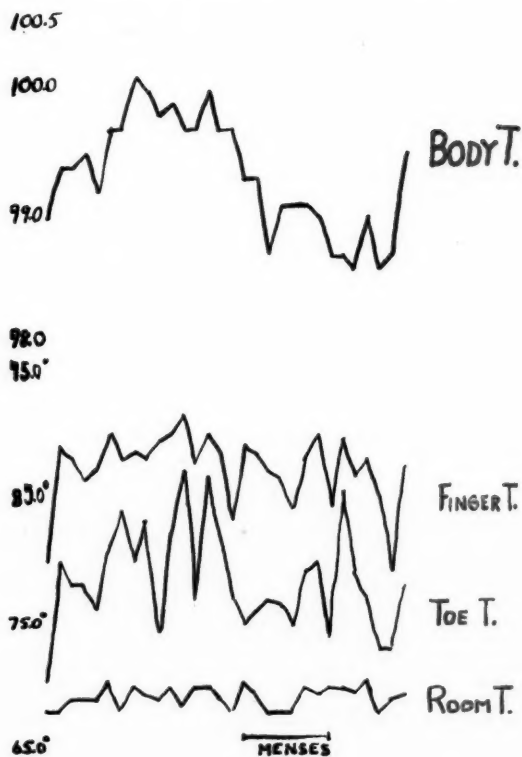


Fig. 2.

Fig. 1.—Index finger P.D. in seven normal menstrual cycles.  
 Fig. 2.—Temperatures recorded throughout a menstrual cycle. The finger and toe temperatures are arithmetic means of both right and left sides.

Fig. 1 indicates the results secured. The polarity of the fingers changed frequently and there is a wide scatter of "peak" days throughout the cycles. "Peak" potential differences exceeded others by only a millivolt or two which is within the field of experimental error for this apparatus.

Snodgrass et al.<sup>18</sup> interpreted the P.D. changes as primarily due to cutaneous vascular conditions with the resultant local temperature one of the major determining factors. Burr found that by heating portions of the saline bridges, a 1 mv. P.D. change was gained for each 2.5° C. temperature differential. In a single subject, it was found that mechanical obliteration of the arterial circulation caused the temperature of the skin of all the digits to fall at approximately the same rate. With skin thermocouples applied to the middle digits, the P.D. between the index fingers was secured during the period of pulse obliteration. The skin temperature fell 1.3° C. for a 1 mv. P.D. change over a span of 5° C.

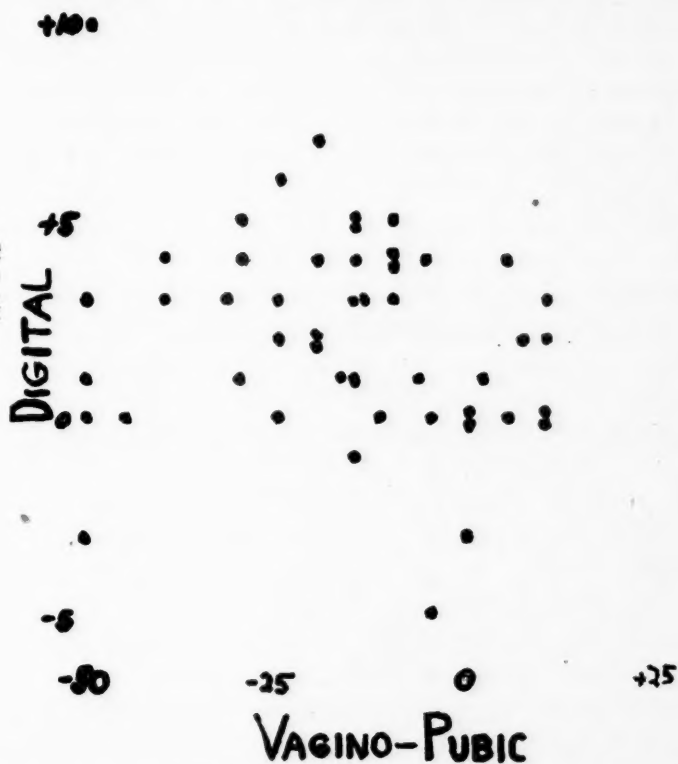


Fig. 3.—Comparison of digital P.D. and vagino-pubic P.D. throughout the menstrual cycle of two patients.

Peculiarly, the P.D. change persisted for twelve minutes after the circulation was restored to normal and the skin temperature returned to the prestriction level. Inasmuch as P.D. is affected by local skin temperature, the skin temperatures of the base of the distal phalanges of both index fingers and great toes and rectal temperatures were taken daily under basal conditions throughout the menstrual cycle of four patients. Fig. 2 presents a typical tracing. Although the finger and toe temperatures fluctuated with the cycle for a span as much as 15° F., the difference between the temperatures of the right and left fingers and toes varied less than 3° F. A difference in skin temperatures cannot therefore be the sole explanation of the observed P.D. changes.

In two patients, the P.D. between mid-vagina and pubis was determined along with the index finger P.D. The midvaginal to pubis potential differences fluctuated widely with multiple peaks and reversals of polarity. Fig. 3 demonstrates such scattering as to call for little correlation between index finger P.D. and vaginal-pubic P.D.

Reboul et al.<sup>20</sup> described typical P.D. shifts with vaginopubic leads in the rat when the follicle was artificially ruptured. In several rats, no shift in P.D. between vagina and pubis could be secured on gross trauma to ovary or uterus. With leads so placed, I have been unable to secure any P.D. shift unless one of the electrodes was placed on the traumatized area.

I share the opinion of Snodgrass et al. that digital P.D. study cannot be used as an index of ovulation in the human being. The vaginal-pubic P.D. in the human being, at present, is not capable of interpretation. To explain the more regular findings in lower animals, the statement of Rogers<sup>16</sup> must be considered, "the rise in P.D. comes at the time of sloughing of vaginal epithelium." His studies were in rats whose vaginal mucosa displays enormous morphologic changes within the estrus cycle. It seems doubtful that the relatively minute morphologic changes in the human vaginal mucosa throughout the menstrual cycle will be reflected in P.D. changes which would exceed the errors of instrumentation. It is difficult to understand how ovulation would affect the skin of the digits in a unilateral manner.

### Summary

With the Schorr-Lamport millivoltmeter method of registering potential, ovulation could not be determined in the human being.

### References

1. Lund, E.: Bioelectric Fields and Growth, University of Texas Press, 1947.
2. Osterhout, W.: Harvey Lectures, p. 169-181, Baltimore, 1930, Williams and Wilkins Company.
3. Beutner, K.: Physical Chemistry of Living Tissues and Life Processes, Baltimore, 1933, Williams and Wilkins Company.
4. Burr, H., Musselman, L., Barton D., and Kelly, N.: Yale J. Biol. & Med. 10: 155, 1937; Science 86: 312, 1937.
5. Burr, H., Taffel, M., and Harvey, S.: Yale J. Biol. & Med. 12: 483, 1940.
6. Barnes, T.: Am. J. Surg. 69: 82, 1945.
7. Langman, L., and Burr, H.: Science 105: 209, 1947.
8. Grenell, R., and Burr, H.: Science 103: 48, 1946.
9. Burr, H., Smith, G., Strong, L.: Am. J. Cancer 32: 240, 1938.
10. Schorr, M., and Lamport, H.: Yale J. Biol. & Med. 18: 307, 1946.
11. Burr, H.: Medical Physics, Otto Glasser, ed., p. 1117-1121, Year Book Publishers, 1944.
12. Burr, H., and Musselman, L.: Yale J. Biol. & Med. 9: 155, 1936; AM. J. OBST. & GYNEC. 35: 743, 1938.
13. Langman, L., and Burr, H.: AM. J. OBST. & GYNEC. 44: 223, 1942.
14. Barton, D.: Yale J. Biol. & Med. 12: 335, 1940.
15. Burr, H., Hill, R., and Allen, E.: Proc. Soc. Exper. Biol. & Med. 33: 101, 1935.
16. Rogers, P.: Am. J. Phys. 121: 565, 1938.
17. Nicholas, J., and Carmosino, J.: Yale J. Biol. & Med. 17: 235, 1944.
18. Snodgrass, J., Rock, J., and Menkin, M.: Am. J. Physiol. 140: 394, 1943.
19. Burr, H.: Yale J. Biol. & Med. 17: 466, 1945.
20. Reboul, J., Friedgood, H., and Davis, H.: Am. J. Phys. 120: 387, 1937.



## A REVIEW OF OVARIAN PATHOLOGY IN 336 LAPAROTOMIES\*

MARY DEWITT PETTIT, M.D., F.A.C.S., PHILADELPHIA, PA.

*(From the Hospital of Woman's Medical College)*

SO MUCH has been written on the diagnosis and pathology of the rare ovarian tumors, that it seemed timely to try to evaluate again the more usual lesions as seen at operation, and to discuss the old argument of conservation versus removal. It seemed that most authors have not stressed sufficiently the multiple gynecologic lesions often found in the same patient, which may radically affect the approach to treatment. Again, some of the largest tumors in the older patients have proved to be benign, while a smaller tumor in a youngish woman proved malignant.

One thousand eighty-six consecutive gynecologic ward admissions to the Hospital of the Woman's Medical College from Jan. 1, 1942, to Jan. 1, 1947, were reviewed. These admissions included entities such as incomplete abortion, lacerations due to childbirth, and the various neoplasms of the female genital tract, plus or minus inflammatory disease. Three hundred thirty-six laparotomies were performed in this series. Vaginal hysterectomies were not included in that number because it has not been our procedure of choice to remove pathologic ovaries by the vaginal route. In 118 of the 336 laparotomies, both ovaries were conserved; in 120 cases, one ovary was saved; in the remaining 98, both ovaries were removed. Definite ovarian changes considered pathologic were reported by the laboratory in 118 of the 218 specimens in which one or both ovaries were removed. The removal of histologically normal ovaries in 100 laparotomies may be accounted for, in most cases, by fear of insufficient blood supply remaining in cases of pelvic inflammatory disease, large multiple myomas, etc. It has been the Department policy, also, to remove both ovaries when panhysterectomy is done for malignancy, in patients where laparotomy has been necessary at or after the menopause, and in selected cases of pelvic endometriosis.

During this five-year period, 10 patients entered the hospital for pathology in an ovary conserved at a previous operation. Eight of these required re-operation and two are still being observed in the Follow-up Clinic. Six of these ten followed operation for pelvic inflammatory disease, one followed operation for endometriosis of the indirect variety. Of these patients, six had their previous operation in this hospital and four elsewhere. The retained ovary caused symptoms within a period varying from five months to seven years after the first operation.

\*Presented at a meeting of the Philadelphia Obstetrical Society, October, 1947.

In the 118 cases with pathologic ovaries, the ovarian abnormality was the reason for operation in 54 patients. Sixty-five cases were operated on primarily for leiomyomas, inflammatory disease, and other entities. Even in the fifty-four cases with the important lesion in the ovary, associated gynecologic abnormalities were found in twenty-seven cases, or exactly half.

Table I shows the various ovarian abnormalities in the 118 cases.

TABLE I. OVARIAN ABNORMALITIES (118 CASES)

	NO.	AGE
Pelvic endometriosis with ovarian involvement	15	18-50
Pseudomucinous cystadenoma, histologically benign	7	42-52
? early malignancy	1	68
Serous cystadenoma, papillary, histologically benign	4	15-71
Cystic tumors, histology indefinite due to necrosis or infection	2	27-38
Fibromas	4	22-52
Angioma	1	46
Dermoid cysts	4	21-35
Follicular cysts, multiple		
History of abnormal bleeding	8	45
No history of abnormal bleeding	37	
Lutein cysts		
Cystic corpora lutea, abnormal bleeding	6	34
Cystic corpora lutea, no abnormal bleeding	14	
Theca lutein cysts, abnormal bleeding	4	
Theca lutein cysts, no abnormal bleeding	9	
Hematoma of corpus luteum with intra-peritoneal hemorrhage	1	
Granulosa cell tumors	2	37-43
Carcinoma—arising in		
pseudomucinous cystadenoma	3	37-68
papillary serous cystadenoma	1	
Solid carcinoma	4	

TABLE II. ASSOCIATED PATHOLOGIC LESIONS

Leiomyomata uteri	58
Pelvic inflammatory disease	32
Endometriosis, direct (adenomyosis)	10
Endometrial abnormality as hyperplasia	19
Prolapsus uteri, severe	4
Ectopic pregnancy	2
Lacerations due to childbirth requiring repair	3
Cervical polyps	6
Parovarian cysts	6
Carcinoma arising (?) in parovarian cyst	1
Sarcoma arising in broad ligament	1

TABLE III. SYMPTOMS IN 54 CASES WHERE OVARIAN PATHOLOGY WAS PRIMARY REASON FOR OPERATING

Nagging pressure or intermittent pain	48
Acute pain, etc., due to torsion	5
Increasing dysmenorrhea	4
Vaginal bleeding	19

TABLE IV. FOLLOW-UP STATISTICS

	NO.	PER CENT
Adequate (over 12 months)	82	69
Partial (less than 12 months)	22	18
No response or lost records	15	12

TABLE V. CARCINOMA FOLLOW-UP (EIGHT CASES PROVED CARCINOMA)

Dead (or presumed dead)	7	(palliative operation 6 bilateral carcinoma) (complete operation 1 unilateral carcinoma)
Living with metastasis	1	(considered operable unilateral carcinoma)
Living with no symptoms or signs metastasis	(1	? malignant, 7 months postoperative)

Of the two cases of granulosa-cell tumor, one has disappeared from our clinics. The other has had a pregnancy in the three-year period, has had to date no known recurrence.

The four cases of fibromas, four cases of dermoid cyst were all unilateral tumors.

The fifteen cases of indirect endometriosis were treated in nine patients by unilateral oophorectomy, in six cases by bilateral oophorectomy. Where the disease was sufficiently advanced to warrant bilateral oophorectomy, postoperative deep x-ray therapy was also given. Thirteen of these patients have been discharged from Follow-up Clinic after observation of over one year; two are still being watched. No recurrence of disease has been found as yet.

### Comment

It is interesting and important, that the angioma, three fibromas, and two of the dermoid cysts which were found at operation and on section of the ovaries in the laboratory, had not been suspected preoperatively. Dr. Theodore Cianfrani at the University of Pennsylvania recently reported seven unsuspected neoplasms on laboratory examination of 1,500 apparently normal-appearing ovaries. A private case of Dr. F. Marian Williams, operated upon during the time covered by our series, proved on section to have a serous papillary cystadenoma 1 cm. in diameter in an ovary 3.5 by 2.0 by 1.2 cm. A photomicrograph of this tumor will show its rather alarming histology. A typical dermoid cyst as shown was removed with tubovarian masses and adhesions typical of chronic pelvic inflammatory disease. A right ovary had a small white nodule at its proximal end (total ovary 4.2 cm. in length) which proved on microscopic examination to be a small angioma, possibly a lymphangioma. This ovary accompanied a large myomatous uterus to the laboratory. These comments should re-emphasize the importance of careful inspection of ovaries under good light at the time of operation. If the blood supply to the adnexa about to be conserved is adequate, and one is planning to leave it in the patient, biopsy of areas which seemed abnormal to either touch or vision should certainly be advocated.

The fact that associated gynecologic lesions were present in 27 of our cases operated upon primarily for ovarian disease is worthy of further comment. Two of our largest pseudomucinous cystadenomas were in postmenopausal women, aged 58 and 68 respectively, who came to clinic primarily because of second degree prolapsus. A similar private patient, aged 68 years, came to me at this same period for bleeding from a pedunculated cervical fibroid. Further examination revealed a pseudomucinous cystadenoma extending to the umbilicus. None of these three women was complaining of her abdominal tumor, two had histologically benign lesions and one had the small area of metaplastic epithelium shown in the slide. No cases of Meigs' syndrome were encountered in the group

of 118 cases and none of the four fibromas reported were apparently hormone producing. In cases with multiple gynecologic lesions, the abdominal approach should be used when ovarian pathology is diagnosed. Advanced age should not in itself discourage the surgeon. We have all had the experience that a vigorous elderly person has proved to be a better risk than a delicate younger one. With modern anesthesia, early ambulation, and adequate supportive therapy, one should try to give the patient comfort in her remaining years. The oldest patient in our series was 71 years old and proved to have a benign serous cystadenoma of large size. In the past eighteen months, peritoneal carcinomatosis was seen from a primary ovarian carcinoma in a white girl of fourteen in the Albany Hospital and a Negro girl of 17 years of age at the Philadelphia General Hospital. One of the most discouraging entities with which we have to deal is primary ovarian carcinoma. It should be emphasized again that the presence of one lesion of the genital tract does not protect the patient from others. We should not relax when the discovery of a polyp may explain vaginal bleeding, or a large cystocele and prolapse may explain pelvic pressure. Silence is characteristic of ovarian neoplasms until complications produce symptoms, by which time cure is often not possible. Whether to remove or conserve ovarian tissue is still at times a most difficult decision. The careful training of every resident in gross and microscopic pathology and in the anatomy of ovarian blood supply cannot be overstressed. One must individualize each case of inflammatory disease and endometriosis on gross findings. Some eminent authorities, such as Dr. Arthur Curtis and the late Dr. John Sampson, have questioned the efficacy of retained ovarian fragments in preventing hormonal difficulties in younger women. A high index of suspicion is probably our greatest safeguard and removal of involuting ovaries at laparotomies near or during the menopause should probably be routine.

### References

1. Crossen, Robert J.: *AM. J. OBST. & GYNEC.* 54: 187, 1947.
2. Curtis, Arthur H.: *A textbook of Gynecology*, ed. 5, Philadelphia, 1946, W. B. Saunders Company.
3. Cianfrani, Theodore: *AM. J. OBST. & GYNEC.* 51: 246-252, 1946.
4. Jacobson, Philip: *Virginia M. Monthly* 73: 63-79, 1946.
5. Mengert, William F.: *Texas State J. Med.* 41: 465-468, 1946.
6. Vara Paavo and Pankamaa Paavo: *Acta obst. et gynec. Scandinav.* 26: 1-78 Suppl. 4, 1946. (Abstract *AM. J. OBST. & GYNEC.* 53: 1058, 1947.)

### Discussion

DR. LEWIS C. SCHEFFEY.—Dr. Pettit's presentation has given occasion for ample discussion of the controversial subject of ovarian conservation.

There is a monument in Rome, Georgia, to an early gynecologist, Robert Battey, whose name is partly remembered for his advocacy, in 1876, of the widespread removal of ovaries for indications ranging from absent uterus with endangered health and absence of menstrual flow to insanity, epilepsy, physical and mental suffering. It was quite the furore of the day. We have come a long way since then. It is not unusual for a young woman, with pain on one side of the pelvis or the other, to give, as a most important point in her history, that of a previous operation for such sort of pain—namely, appendectomy and removal or partial resection of one or both ovaries. Most of these patients have been first operated upon by sev-



eral surgeons, but gynecologists are not guiltless either. In the vast majority of such instances unrecognized follicular or corpus luteum cysts have been ignorantly regarded as offending neoplasms, and a vital gonad has been sacrificed or damaged.

Now the question in my mind is that, when we are operating to correct pelvic pathology, we should not remove ovaries that appear and feel normal; and the presence of tiny cystic elevations is usually normal. Neither do I see how we can simply draw an arbitrary line at any particular age regarding ovarian removal. What we elect to do depends upon individualization of the patient at hand. In all my experience at Jefferson Hospital, I have only once encountered malignant change in conserved ovaries.

Naturally, in pelvic malignancy, all the pelvic organs should be removed, and perhaps in women of the older age group, conservation of apparently normal ovaries would not be so important. Certainly, however, there are many instances in which ovarian conservation is followed postoperatively by much less vasomotor disturbance than when the ovaries have been removed. Even when technical reasons require ovarian removal, it is possible to use some healthy ovarian tissue by resecting it from the removed ovary and transplanting it beneath the rectus fascia, or even by allowing it to remain in situ in the neighborhood of the infundibulopelvic ligament. These bits of ovarian tissue seem to function well, and such procedures are worth while when ovaries cannot be left in situ as is so often the case when dealing with chronic pelvic inflammatory disease.

It has been mentioned that careful inspection of the ovaries may reveal the possibility of the presence of a true neoplasm, small in size, and, in such instances, I agree that it is good practice to bisect the ovary and resect such a localized tumor. I have done this on several occasions, and twice I have been rewarded by finding, 1, a tiny dermoid, and 2, a luteoma.

I think that every ovary visualized shows a number of cysts, but they are usually retention cysts and are nonneoplastic. One of the points that we constantly impress upon our students is to study the classification of cystic enlargements of the ovary, emphasizing the difference between nonneoplastic cysts of the ovary, which are functional, and true neoplastic cysts, which may be benign or malignant. Practitioners, too, should be well informed in this respect.

DR. CLAYTON T. BEECHAM.—Today we all agree that the female pelvis in general, and the ovary in particular, receive a high degree of surgical assault and abuse. This is not warranted, but the attack continues unabated. Dr. Pettit mentioned 79 cases that were diagnosed as pathologic ovaries and had nothing more than follicular or lutein cysts. I have never seen a normal ovary that did not have normal follicular cysts in it. I sincerely wish the surgeons of Philadelphia and of America would cease to regard the follicular cyst as a surgical entity. I do not see any reason for their removal and cannot agree with their removal because of bleeding. The cause of bleeding is not from follicular cysts but from endocrine imbalance.

Mention has been made of Crossen's advice for removal of normal ovaries at age 43 or more in all women having pelvic laparotomies. A few years ago he had a lower age limit, i.e., 40. One famous gynecologist said years ago that no woman needed her ovaries except a neurotic individual. Then recently, another well-known gynecologist stated that a woman over 35 does not need her ovaries. Such an understanding of ovarian function and female endocrinology is a little hard to understand. Yet, unfortunately, it is in everyday use in this country. I would say, if we are going in for prophylactic surgery against cancer, why take on such an uncommon malignancy. I have not heard Crossen propose bilateral mastectomy for women because they are on an operating table and over 43 years of age. We looked up the last thousand gynecologic admissions to our private service and found unilateral or bilateral oophorectomy for neoplastic disease of the ovary in thirty-four instances. Five of these cases were malignant. From my own figures, I have disregarded Crossen's remarks and believe they have been given too much publicity. Many things have been handed down to us in all branches of medicine and they constitute nothing more than the perpetuation of error.

Dr. Pettit mentioned inoperable carcinoma of the ovary. Frequently x-ray renders these patients operable. Since x-ray does not kill the cancer they should have a panhysterectomy and bilateral salpingo-oophorectomy. Some of these patients will survive in spite of extensive involvement.

Dr. Pettit brought up the subject of unsuspected ovarian pathology discovered in normal appearing ovaries that have been removed. One naturally wonders if the ovaries were really normal to inspection and palpation. At Philadelphia General Hospital, the standard treatment for years in pelvic inflammatory disease has been a complete ablation of the pelvic organs. (There is more of an attempt at conservatism today.) In this vast source of material, ovaries were predominantly cystic and neoplastic disease in such instances was not noted.

The best guide a surgeon can have today as to the necessity for oophorectomy is provided in Novak's classification of ovarian tumors. Novak divides the ovarian enlargement into nonneoplastic and neoplastic groups. In the nonneoplastic group he has listed the follicular, lutein, germinal inclusion and endometrial cysts. With the exception of the endometrial growth, surgery is unnecessary in this group.

DR. PETTIT (Closing).—I had hoped my paper would cause some reactions and it did. I think I would like, in view of the discussions, to point out to the audience that I made on my charts the differentiation between the cystic ovaries which were accompanied by abnormal bleeding and those which were not. I did that for the purpose of bringing out points in the discussion which have come up. I think we are agreed, fundamentally, that we wish to be conservative and I think we all are removing fewer cystic ovaries than were taken out formerly. The associated pathology explains some of those cystic ovaries. Those with abnormal function are not always identifiable histologically. We all know that ovarian adhesions are likely to be the site of cyst formation. There were 32 cases of inflammatory disease which cuts down some on our apparent delinquency. In a series of cases taken consecutively with a large number of operators, our statistics are conservative compared with recent reports in the country at large. Concerning surgery in carcinoma of the ovary, by palliative surgery I did not mean that attempts were not made to remove all possible carcinomatous tissue, I meant that ascites and local extension were already present and extensive. I believe as you do, Dr. Beecham, that major surgery should be done on these case if possible. Unfortunately, in this particular group, we were unlucky because x-ray therapy plus surgery did not get these patients into an operable state. It was a fact that they were seen too late.

## THE CLINICAL USE OF SODIUM VINBARBITAL BY THE INTRAVENOUS ROUTE IN OBSTETRICS\*

LOUIS G. FOURNIER, M.D., SYRACUSE, N. Y.

(From the St. Joseph's Hospital)

**S**ODIUM vinbarbital† is a soluble barbiturate provided in capsules for oral administration and in sterile solution for intravenous use. It is classed as a sedative, hypnotic, and analgesic agent. This drug has a wide margin of safety. Its action is of short duration and it is relatively free of undesirable side-effects such as excitation or "hang-over."

The pharmacology and toxicology of this barbiturate have been investigated by a number of workers,<sup>1-4</sup> particularly with respect to its effect on blood pressure and respiration, and it appears that sodium vinbarbital is a relatively nontoxic compound when employed in therapeutic doses. It has the advantages of rapid action and low toxicity, and causes no depression of the respiratory or cardiac centers. The drug is largely detoxified in the liver.

Many hospitals, including ours, have not the resident staff that is almost a necessity for the proper administration and guidance of the more complicated routines in labor for the relief of pain and mental stress. Favorable reports on the oral and intravenous usage of Vinbarbital sodium by Prince, Evans, Bernstein, and Lewis brought us to the study and usage of Vinbarbital sodium intravenously at St. Joseph's Hospital. If this method combined a wide margin of safety for both the mother and baby with satisfactory amnesia, analgesia, and anesthetic effects combined with utter simplicity of administration, we felt we would have a drug and method highly advantageous to our needs.

With these factors in mind a study of the intravenous administration of sodium vinbarbital during labor was undertaken. The material presented represents 500 unselected patients from the private service at St. Joseph's Hospital. Since our only past experience with intravenous barbiturate derivatives had been with drugs such as pentothal, precautions were observed with respect to dosage at the beginning of this study until the results to be anticipated with this particular preparation could be ascertained. The dosage then was gradually increased until the present satisfactory dosage levels were established.

The cases reported here have been divided into two groups of 250 patients each. In Group One no attempt was made to deliver under intravenous sodium vinbarbital anesthesia alone, except in those instances in which routine usage

\*Presented before the Central New York Association of Obstetricians and Gynecologists, Syracuse, N. Y., Sept. 30, 1947, and the Obstetrical and Gynecological division of the Rochester Academy of Medicine, Rochester, N. Y., Dec. 16, 1947.

†Sodium vinbarbital is the nonproprietary name for sodium 5-ethyl-5- (1-methyl-1-butenyl) barbiturate, and is distributed under the name of Delvinal sodium vinbarbital. The material used in this study was provided through the courtesy of the Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pennsylvania.

of this drug for amnesia and analgesia was found to be sufficient for delivery also. When necessary, delivery was completed under ether, gas-oxygen, or local anesthesia. In Group Two a deliberate attempt was made to complete delivery under intravenous sodium vinbarbital alone without any supplemental anesthesia.

The patients in Group One comprised 145 primiparas and 105 multiparas, ranging in age between 18 and 45 years. Presentation and position in this group were 12 breech and 234 vertex (left occipitoanterior 115, right occipitoanterior 107, left occipitoposterior 4, and right occipitoposterior 8).

#### Method of Administration

The method of administration in this group as a rule was uniform. Demerol (meperidine) and scopolamine were administered when active labor was in progress with uterine contractions four to five minutes apart, or when the cervix showed at least two fingerbreadths dilatation. The initial dosage was  $1\frac{1}{2}$  grains of Demerol and  $\frac{1}{100}$  grain of scopolamine;  $\frac{1}{200}$  grain of scopolamine was given one-half hour later. Either Demerol or scopolamine or both were repeated as indicated as labor progressed. Sodium vinbarbital was administered intravenously when the cervix was fully dilated in both primiparas and multiparas, and was repeated as necessary if restlessness with pains occurred at any time prior to the completion of labor. Occasional restlessness due to the administration of Demerol and scopolamine was controlled by the intravenous administration of sodium vinbarbital before full dilatation had occurred.

Forty-three patients in Group One, or 17.2 per cent, received no preliminary medication, as they entered the hospital well advanced in labor and ready for intravenous sodium vinbarbital. These 43 patients were "screaming" multiparas; sodium vinbarbital is an excellent drug for this group, since the patient is asleep in the course of two minutes and is well under control for proper preparation and delivery.

At the beginning of this study sodium vinbarbital was injected intravenously in an initial dose of 4 or 5 grains, but as our experience with this drug became more extensive the dosage was increased so that it is now routine practice to give an initial dose of 10 grains followed by 5 or 10 grain doses as indicated until completion of labor. It is at this point that failures will occur with the intravenous use of this barbiturate if an insufficient dosage is employed. Before full acquaintance with the drug is achieved there is a tendency to hesitate to give the full 10 grain dose intravenously, since the patient may appear to be well sedated and asleep after 5 or 6 grains have been injected.

In the present study an attempt was made to individualize dosage (Table I). However, this has been found to be unnecessary and, in fact, it is less advantageous to individualize the initial dose. A routine initial dose of 10 grains, irrespective of the body weight of the patient, has been found to be the most satisfactory method. Subsequent dosage then is individualized and regulated by the response of the patient, as gauged by restlessness with pain. The ideal reaction to uterine contractions while under this drug manifests itself simply in increased respiration with a snoring sound, but with no movements except a bearing down effort. When the patient exhibits a desire to roll over or move her arms and legs in a restless manner with pains, it is an indication for further medication then or relatively soon. This has been observed to be the best criterion for further medication in this group and is without danger.

The length of labor before any medication was given varied from one hour to seventeen and one-half hours. The elapsed time between preliminary medica-



tion and intravenous sodium vinbarbital ranged from ten minutes to thirteen and one-half hours. In the primiparous group 56 per cent received Demerol and scopolamine over two hours before intravenous sodium vinbarbital therapy and 35 per cent less than two hours before the latter. In the multiparous group 20 per cent were given Demerol and scopolamine two hours or more before the barbiturate and 80 per cent under two hours.

TABLE I. DOSAGE OF SODIUM VINBARBITAL

NO. OF PATIENTS	PERCENTAGE OF TOTAL PATIENTS	TOTAL DOSAGE*
3	1.2%	20 grains
1	0.4%	16 grains
20	8.0%	15 grains
4	1.6%	13 grains
5	2.0%	12 grains
147	58.8%	10 grains
67	26.8%	8 grains
2	0.8%	7 grains
1	0.4%	6 grains

\*In this group 215 patients were given a single intravenous dose of sodium vinbarbital and 35 patients received 2 or more doses.

The period between intravenous sodium vinbarbital administration and delivery varied from five minutes to eleven hours. Delivery occurred in 70.8 per cent of the primiparas under two hours and in 29.2 per cent over two hours. In the multiparous group 93.2 per cent delivered under two hours, and 6.8 per cent over two hours. These results tend to corroborate the impression that uterine contractions were not diminished or delayed by the use of this drug and labor was not prolonged. In fact, in many instances labor progressed much more rapidly after administration of intravenous sodium vinbarbital. The response to rectal or perineal pressure with bearing down effort was good under this therapy.

The elapsed time between the onset of labor and the intravenous administration of sodium vinbarbital, the elapsed time between preliminary medication and sodium vinbarbital intravenously, or the elapsed time between administration of the barbiturate and delivery did not in any way affect the progress of labor or the reaction of the mother or baby. This is an important point, since sodium vinbarbital can be given intravenously at any time without fear of harm to mother or infant because of poor timing or an inadequate time interval.

The data presented in Table II show that over 70 per cent of patients received intravenous sodium vinbarbital therapy at full dilatation. This routine was adopted for the sake of uniformity in this study and also because the majority of patients were comfortable at this point with preliminary medication. However, the drug can be administered at any stage of dilatation with satisfactory results.

TABLE II. INTRAVENOUS SODIUM VINBARBITAL MEDICATION WITH RELATION TO DILATATION

PRIMIPARAS	MULTIPARAS	PERCENTAGE OF PATIENTS	FINGERBREADTHS DILATATION
121	63	73.6%	Full
11	7	7.2%	4½
9	23	12.8%	4
4	10	5.6%	3
0	2	0.8%	2½
145	105		

The intravenous medication in this series was given by the author, by the various interns in the hospital, the graduate nurses on duty, and medical stu-

dents. No special knowledge or skill was required except the ability to insert a needle in a vein. Any available vein in the upper or lower extremities was used. A 10 c.c. syringe with a 20-gauge needle was employed, and approximately one and one-half minutes were allowed for the injection of 10 c.c. of solution containing one grain of sodium vinbarbital per cubic centimeter. The rapidity and ease of action are remarkable; deep sleep accompanied by deep, regular breathing with good color occurred in the majority of patients before the injection was completed. Restlessness can be avoided entirely by adequate dosage. Additional intravenous sodium vinbarbital medication is given when restlessness with pains is observed, and there has been no evidence in any instance of overdosage with the use of this method.

There was no apparent effect on the duration of labor. Uterine contractions were not diminished in intensity or in rate. Dilatation progressed rapidly, and a large percentage of patients showed a good bearing down action.

### Effect on the Mother

Sedation was classified as complete, incomplete, or failure. Complete sedation was obtained in 132 primiparas and 94 multiparas, a total of 226 patients (90.4 per cent). In the restless group of 14 primiparas and 7 multiparas, a total of 21 patients (8.4 per cent) in whom sedation was incomplete, full amnesia was obtained but the patients were restless with pains and difficult to control. Three multiparas (1.2 per cent) were classified as failures with respect to sedation. These patients were drowsy but did not go to sleep, and remembered scattered incidents after therapy. With our present knowledge it is believed that a larger initial dose of sodium vinbarbital or more adequate supplemental administration of the drug would have controlled the restless patients and those in whom sedation was not obtained. Twenty of the group of 24 patients in whom sedation was classified as incomplete or failure were among the first studied and these patients received an inadequate initial dose of sodium vinbarbital. In the remaining four patients the initial dose of 10 grains was satisfactory, but a supplementary dose was not given or was inadequate. There have been no restless cases or failures among the last 175 cases studied in this group of 250.

Additional anesthesia for delivery or repair was not required in 66 primiparas and 55 multiparas, a total of 121 patients (48.4 per cent) beyond the routine intravenous administration of sodium vinbarbital, although no attempt was made in this group to deliver with the use of this drug alone. A small amount of inhalation anesthesia was needed for delivery but none for repair in 44 primiparas and 32 multiparas, a total of 76 patients (30.4 per cent). Either regular inhalation anesthesia or local anesthesia was employed in the remaining 35 primiparas and 18 multiparas, a total of 53 patients (21.2 per cent) for delivery and repair.

In other words, nearly 50 per cent of this group obtained anesthesia effect sufficient for delivery and repair, although this was not deliberately attempted in this group. Another 30 per cent were repaired without further anesthesia. Only 21 per cent required full anesthesia.

The maternal blood pressure was checked before the intravenous administration of sodium vinbarbital and every twenty to thirty minutes thereafter until delivery. There was no change in blood pressure of any significance except in four cases, and these were not alarming changes. In one of these patients there was a slight rise in blood pressure, and in the remaining three a slight drop. These minor changes were transitory and of short duration.

Respiration was not affected in any case. Respirations remained full, regular, and at the rate of 18 to 20 per minute. Occasionally, because of com-

plete relaxation, the tongue fell against the roof of the mouth impeding the air passages. When this occurred, the usual metal airway was inserted.

The only significant pulse changes noted were in nine cases. The change was a slowing of the pulse rate with no alteration in character otherwise or no change in heart sounds or rhythm. This change was of short duration with a return to the original rate. This effect is sometimes noted with Demerol alone.

Every woman in this series was questioned as to her memory of labor and delivery. In 99 per cent there was complete loss of any recollection of events from the intravenous administration of sodium vinbarbital until some hours after delivery. All patients slept from one to six or eight hours following delivery. Sleep was quiet, deep, and restful; on awakening the patients felt refreshed and there were no complaints of "hang-over." No restless patients were encountered in this post delivery period. There was no instance of nausea or vomiting and no apparent contraindication to the intravenous use of sodium vinbarbital. All patients were satisfied with their experience and expressed a desire for this type of medication in the future.

#### Effect on Infants

The data on fetal mortality are presented in Table III. Of the six still-born infants, four died prior to admission of the mother to the hospital. These were the monstrosity, the erythroblastotic infant, and eight-month twin with velamentous insertion of the cord, and the complete abruptio placentae at seven months. These four deaths can in no way be attributed to the use of sodium vinbarbital. Two infants died during labor, one had a true knot of the cord, and the second one, a ruptured umbilical cord vessel from an anomaly of the cord. These deaths likewise were not attributable to the intravenous barbiturate therapy. Medication also was not a factor in the four neonatal deaths of premature twins. The neonatal death due to congenital atelectasis cannot be definitely proved one way or the other to have been affected by the barbiturate, since an autopsy was not permitted. However, the impression was obtained that this death was not influenced by medication. The infant breathed and cried spontaneously and immediately, but the breathing was obstructive in type, and true thoracic breathing was never established. It is believed that this baby might have been saved by bronchoscopy.

A change in the fetal heartbeat was noted in only four instances in this series, and was characterized by an increase from 140 to 160 or 170 for a short period. All four of these babies survived.

Considerable care was exercised in collecting data with respect to the effects of medication on the infant. Those infants who cried spontaneously were not considered to have any asphyxia. Infants who needed only the clearing of the air passages were classified as mildly asphyxiated. Infants who in addition required carbon dioxide and oxygen were considered to be moderately asphyxiated. No respiratory stimulant other than carbon dioxide and oxygen was required in any infant. The color of all the babies was good, and no great difficulty was encountered in establishing respiration in any group. A further breakdown of the 19 babies classified as moderately asphyxiated (Table IV) revealed that in 13 of these other factors were involved, such as a long hard labor, partial separation of the placenta, midforceps delivery, or version complicating the picture and contributing to fetal embarrassment. The elapsed time between administration of sodium vinbarbital and delivery or the size of barbiturate dosage did not appear to play any part in the incidence of asphyxia in this series.

Group Two comprised 250 patients in whom a deliberate attempt was made to deliver under intravenous sodium vinbarbital alone without supplemental anesthesia.

TABLE III. FETAL MORTALITY (GROUP ONE)

Total number of babies delivered		256
Stillbirths	6	
1 true knot		
1 abruptio placentae at 7 months		
1 twin with velamentous insertion of the cord		
1 monstrosity		
1 7½ month erythroblastotic infant		
1 anomaly of umbilical cord		
Neonatal deaths	5	
2 6 month twins, lived 1 and 2 days		
2 6½ month twins, lived 6 days		
1 congenital atelectasis		
Total number of infants lost	11	
Gross fetal mortality		4.3%
Corrected fetal mortality (5 neonatal deaths)		2.0%

TABLE IV. EFFECT OF MEDICATION ON 250 LIVING INFANTS

DEGREE OF ASPHYXIA	NUMBER OF INFANTS	PERCENTAGE OF INFANTS
None	200	80.0%
Mild	31	12.4%
Moderate	19	7.6%
	250	

### Method of Administration

The routine for intravenous administration of sodium vinbarbital in this group was identical with that of the previous group of patients, except that at the time of delivery additional sodium vinbarbital was given if sedation was not sufficient for delivery. A total dosage of from 10 to 25 grains (average 15 grains) of sodium vinbarbital was administered intravenously (only one patient received the maximum total dosage of 25 grains). Ten grains of the barbiturate were given routinely as the initial dose at full dilatation, and medication was repeated in 5 to 10 grain doses as necessary.

This group contained 129 primiparas and 121 multiparas. There was 236 cephalic presentations and 14 breech. One hundred six were right occipitoanterior; 111 were left occipitoanterior; 6 were left occipitoposterior; and 13 were right occipitoposterior.

Spontaneous delivery showed 37 primiparas and 50 multiparas. Low forceps showed 93 primiparas and 61 multiparas. Midforceps were used in four primiparas and one multipara. High midforceps were used in two primiparas.

Rotation of the posterior head was done in ten cases, two cases by manual rotation and eight cases by the use of forceps.

One hundred sixty-seven cases had episiotomy and repair performed.

One case of Dührssens incisions of the cervix and one case of Piper forceps in the aftercoming head.

### Effect on the Mother

Satisfactory amnesia and anesthesia were obtained with the intravenous use of sodium vinbarbital and no supplemental anesthesia with other agents was required in 246 of these patients (98.2 per cent). Two patients who received a total dosage of 15 and 20 grains of the barbiturate, respectively, were too restless for delivery, and anesthesia was completed with ether. One patient was given ether to control delivery of the head because of a previous rectovaginal fistula. In a fourth patient version was contemplated and ether was given



to relax the uterus completely. Thus there were actually only 2 failures, not with respect to analgesia and amnesia but with regard to full anesthesia, and the percentage of patients obtaining complete sedation then was 99.1 per cent.

### Effect on Infants

A total of 252 babies were born to these 250 mothers. No difference from the previous group was observed with respect to the necessity for resuscitation of infants. The administration of sodium vinbarbital for delivery did not increase the incidence of either mild or moderate asphyxia in this group. The data on fetal mortality are given in Table V.

TABLE V. FETAL MORTALITY (GROUP TWO)

Total number of babies delivered		252
Stillbirths	3	1.19%
(1) contracted pelvis, long labor, late cesarean with death of fetus during operation		
(2) macerated fetuses, dead before admission of mother to hospital		
Neonatal deaths (all premature)	6	2.38%
1 7-month infant, 2½ lb., lived 2 days		
1 7-month infant, 2 lb. 4 oz., lived 24 hrs.		
1 5-month infant, lived few hours		
2 5½-month twins, lived 2 hours		
1 8-month toxic infant, lived 5 days		
Total number of infants lost	9	
Gross fetal mortality		3.57%
Corrected fetal mortality (6 neonatal deaths)		1.19%

Two macerated fetuses dead before admittance to the hospital cannot be attributed to medication. The third stillbirth was distinctly a case that should have been sectioned earlier, and fetal death occurred during cesarean section. This case undoubtedly died because of cerebral damage. In the neonatal group three babies were nonviable infants of five and one-half months. Three babies were six and one-half to seven months prematures weighing less than 3 pounds and toxic. All these babies lived long enough to excuse the barbiturate of complicity, I believe. It will be noted that the increased dosage and of necessity late final dosage for delivery did not alter the fetal mortality rate in this group over the previous group.

There was no maternal mortality in these 500 cases.

### Summary and Conclusions

1. In the study presented herein, 500 patients received sodium vinbarbital intravenously for obstetric amnesia, analgesia, and anesthesia.
2. A total of 508 infants was delivered with a gross fetal mortality of 3.9 per cent and a corrected fetal mortality of 1.3 per cent. No fetal death could be attributed to the use of this drug. There was no maternal mortality.
3. Complete amnesia and analgesia were obtained in 497 patients (99.4 per cent). Anesthesia was satisfactory for delivery in 246 patients (98.4 per cent) in whom this effect was attempted.
4. The intravenous administration of sodium vinbarbital is a simple procedure, requiring no special skill. Induction of sleep was almost instantaneous; there were no "hang-over" symptoms, patients awakening rested and

refreshed. Restlessness was not a common feature. When it occurred, further intravenous administration of sodium vinbarbital effectively controlled it.

5. General anesthesia when indicated was not complicated by the previous use of sodium vinbarbital.

6. Uterine contractions were unaffected by the use of this barbiturate. Labor was not prolonged, and postpartum hemorrhage did not occur in this series.

7. It is recommended that an initial dose of 10 grains (0.6 Gm.) be administered routinely. Subsequent doses of 5 or 10 grains (0.3 or 0.6 Gm.) then are given when restlessness is evident with uterine contractions.

8. The results indicate that sodium vinbarbital, administered intravenously, is a very satisfactory drug for the induction of obstetric amnesia, analgesia, and anesthesia.

*Note.*—An additional 500 patients have been delivered, since this paper was submitted, with comparable results.

#### References

1. Hendrix, J. P.: J. Pharmacol. & Exper. Therap. **68**: 22, 1940.
2. Carmichael, E. B., and Thompson, W. D.: Proc. Soc. Exper. Biol. & Med. **46**: 233, 1941.
3. Peoples, S. A., and Carmichael, E. B.: Proc. Soc. Exper. Biol. & Med. **48**: 381, 1941.
4. Holck, H. G. O., Weeks, J. R., Mathieson, D. R., and Duis, B.: J. Am. Pharm. A. (Scient. Ed.) **32**: 180, 1943.
5. Bernstine, J. B., and Prince, L. N.: AM. J. OBST. & GYNEC. **45**: 851, 1943.
6. Evans, J. R.: AM. J. OBST. & GYNEC. **47**: 821, 1944.
7. Lewis, M. S.: AM. J. OBST. & GYNEC. **51**: 395, 1946.

STATE TOWER BUILDING.

## A CLINICAL EVALUATION OF DIENESTROL IN THE CLIMACTERIC

JOSEPH G. VIVIANO, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, St. Louis University)

**D**IHYDROXI-DIPHENYL-HEXADIENE, commercially known as dienes-  
trol,\* was first discovered to have estrogenic activity by Dodds and his  
associates in 1938.<sup>3</sup> At this time, the work done with the drug was restricted  
to animal experiments. These investigators determined, using castrate female  
mice, that 100 per cent estrus could be produced with a dosage of 3 gammas of  
dienestrol by mouth, while with diethylstilbestrol only 70 per cent estrus was  
obtained. Emmens<sup>4</sup> determined in similar experiments that dienes-  
trol by mouth produced results comparable to four times the amount of diethylstilbestrol. Due  
to the difficulty and the expense of synthesis of the drug, no further investigation  
was carried out at that time.

Recently the development of an easier and cheaper method of synthesis has  
resulted in further investigation of its clinical properties. In 1938, Barnes<sup>1, 2</sup>  
investigated a group of menopausal patients, and determined that a dosage of  
0.1 mg. twice daily was sufficient to relieve menopausal symptoms. Senile  
vaginitis and concurrent symptoms were relieved in several cases. None of these  
patients exhibited any symptoms of intolerance.

Finkler and Becker,<sup>5, 6</sup> in 1946, in a series of seventy-three patients in the  
climacteric, determined that there was a high incidence of relief of symptoms and  
a very low incidence of toxicity on dosages of 0.2 to 1.5 mg. per day.

Sikkema and Severinghaus,<sup>13</sup> also in 1947, in a series of twenty-one patients,  
reported similar findings and suggested optimum dosages of 0.1 to 0.6 mg. per  
day. There were no toxic effects.

Rakoff, Paschkis, and Cantarow,<sup>11</sup> using the drug in forty menopausal  
women, determined the dosage range from 0.1 to 1.0 mg. per day with no symp-  
toms of intolerance.

### Method of the Present Study

A clinic was established for menopausal patients at Firmin Desloge Hospital  
in St. Louis, and all patients who complained of symptoms which might be due  
to the climacteric were referred for evaluation and treatment. The patient, on  
her initial interview, was questioned and an evaluation was made. Those patients  
who seemed to have predominating psychic factors were eliminated from the  
study. Those patients with organic disease whose symptoms might simulate  
those of the climacteric were also eliminated.

The patients who were chosen for the study were examined gynecologically  
and a vaginal smear was made. They were started on dienes-  
trol at a dosage of 0.1 mg. per day. The patients were seen weekly and questioned as to symp-  
toms. Each week the dosage was increased until symptoms reached a constant  
minimum level. Each week a vaginal smear was taken. The dosage increase  
was usually by 0.1 mg. per day each time the patient was seen. In a few  
patients, in whom it was obvious after a short time that larger doses were

\*Dienestrol was supplied by White Laboratories, Inc.

going to be necessary, the rate of increase was more rapid. The vaginal smears were repeated until full estrogen effect was observed or until the symptoms had reached their minimum level.

The vaginal smears were stained with Shorr's<sup>12</sup> stain. The patients were classified into four groups depending on the severity of their symptoms. A similar classification has been used by Fluhmann.<sup>7</sup> The vaginal smears were graded as Reaction 1, 2, 3, or 4, as described by Geist and Salmon.<sup>8</sup> Reaction 1 represented complete estrogen deficiency and was characterized by a predominance of basal cells with leucocytes, erythrocytes, and debris. Reaction 4 represented full estrogen effect with large flat cells with pyknotic nuclei, leucopenia, and no debris. Reactions 2 and 3 are intermediates between these two extremes.

### Results

#### GROUP I—13 PATIENTS

##### RELIEF OF SYMPTOMS:

Partial 1

Satisfactory 12

MINIMAL EFFECTIVE DOSE	NO. OF PATIENTS
0.2 mg. per day	1
0.3 mg. per day	2
0.4 mg. per day	3
0.5 mg. per day	3
1.0 mg. per day	3
1.5 mg. per day	1

#### GROUP II—7 PATIENTS

##### RELIEF OF SYMPTOMS:

Partial 2

Satisfactory 5

MINIMAL EFFECTIVE DOSE	NO. OF PATIENTS
0.2 mg. per day	1
0.3 mg. per day	2
0.4 mg. per day	3
1.0 mg. per day	1

#### GROUP III—4 PATIENTS

##### RELIEF OF SYMPTOMS:

Partial 0

Satisfactory 4

MINIMAL EFFECTIVE DOSE	NO. OF PATIENTS
0.4 mg. per day	1
0.5 mg. per day	2
1.5 mg. per day	1

#### GROUP IV—7 PATIENTS

##### RELIEF OF SYMPTOMS:

Partial 2

Satisfactory 5

MINIMAL EFFECTIVE DOSE	NO. OF PATIENTS
0.5 mg. per day	1
1.0 mg. per day	2
1.5 mg. per day	2
2.0 mg. per day	2



### Summary and Discussion

Fifty-nine patients were treated in the clinic. Of these, thirty-one are reported. The remaining twenty-eight were eliminated because of irregular attendance and failure to use the medication as prescribed. Of the reported group, four were premenopausal, sixteen had experienced a spontaneous menopause, and eleven had experienced a surgical menopause. Of the reported group, 84 per cent were satisfied with the relief provided by dienestrol. The remaining 16 per cent admitted partial relief but not complete satisfaction.

From the above tabulations, it can be seen that, as the severity of symptoms increases, the dosage necessary for maximum relief increases. This, of course, is not true in all cases, but there is a definite trend in that direction. The dosage range is from 0.2 mg. per day to 2.0 mg. per day. The majority fall into a range of 0.4 mg. per day to 1.5 mg. per day. An occasional patient requires more or less. Nineteen of the thirty-one were maintained with satisfaction on 0.5 mg. per day or less, six more between 0.5 mg. per day to 1.0 mg. per day and seven needed 1.0 mg. per day to 2.0 mg. per day. Because of the discrepancy between these doses and those previously reported, attempts were made to decrease the dosage in those patients who were taking 1.5 to 2.0 mg. per day. Invariably these attempts resulted in recurrence of symptoms.

Thirty of the thirty-one patients exhibited full estrogen effect in their vaginal smears, which, in almost all cases, occurred together with or soon after maximum relief of symptoms.

Of the total group, one patient experienced nausea and vomiting on a dosage of 0.5 mg. per day. The drug was discontinued for one week and restarted at the level of 0.3 mg. per day with no further evidence of toxicity. Of the total group, two patients exhibited withdrawal bleeding. One of these was a twenty-seven-year-old castrate who had on several occasions received estrogen therapy of various types. Several times during these courses of treatment she bled severely. Twice the bleeding was so profuse that a dilatation and curettage were deemed necessary. After stabilization on dienestrol at the level of 2.0 mg. per day, she was placed on intermittent courses of treatment of twenty days with a ten-day interval. During each ten-day interval, she experienced withdrawal bleeding which simulated a normal menstrual period. The other patient who bled was sixty-three years old, twenty years postmenopausal. This patient voluntarily stopped taking medication for a period of one week. During this period she spotted for one day.

Of the total group, there was no patient who felt that dienestrol was totally ineffective.

### Conclusions

1. Dienestrol is an active estrogenic substance. It is efficient in the treatment of the symptoms of the climacteric and produces vaginal changes characteristic of any estrogenic substance.
2. The optimum dosage of dienestrol varies with the individual. Dosages of 0.2 to 2.0 mg. per day were given during the course of this study. Speaking generally, the dosage of dienestrol parallels the severity of the symptoms.

3. Dienestrol produces an unusually low number of toxic effects and, as far as this study is concerned, none that were not easily controlled.

### References

1. Barnes, J.: Brit. M. J. 1: 601, 1942.
2. Barnes, J.: Brit. M. J. 1: 79, 1944.
3. Dodds, E. C., Lawson, W., Goldberg, L., and Robinson, R.: Proc. Royal Soc., London 127: 140, 1939.
4. Emmens, C. W.: J. Physiol. 94: 22, 1939.
5. Finkler, R. S., and Becker, S.: AM. J. OBST. & GYNEC. 53: 513, 1947.
6. Finkler, R. S., and Becker, S.: J. Am. Med. Wom. Assn. 1: 152, 1946.
7. Fluhmann, C. F., and Murphy, K. M.: AM. J. OBST. & GYNEC. 38: 778, 1938.
8. Geist, S. H., and Salmon, U. J.: AM. J. OBST. & GYNEC. 38: 392, 1938.
9. Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Uterine Cancer by Vaginal Smear, New York, 1943, Oxford University Press.
10. Papanicolaou, G. N., and Shorr, E.: AM. J. OBST. & GYNEC. 31: 806, 1936.
11. Rakoff, A. E., Paschkis, K. E., and Cantarow, A.: J. Clin. Endocrinol. 7: 688, 1947.
12. Shorr, E.: Science 94: 545, 1941.
13. Sikkema, S. H., and Severinghaus, E. L.: Am. J. Med. 2: 251, 1947.
14. Smith, A. E. W., and Williams, P. C.: Nature 143: 718, 1945.

## REPORT ON 510 CASES OF CLASSICAL CESAREAN SECTION\*

A. C. WILLIAMSON, M.A., M.D., F.A.C.S., PITTSBURGH, PA.

(From the Obstetrical Clinic of the Western Pennsylvania Hospital)

WE ARE presenting this report of sections from a controlled clinic in which the patients are closely watched and decisions made, for the most part, well in advance of section. The operations were largely performed by the author and his associates, Drs. Loughrey, Ingram, and Huff, trained in and confining their work to obstetrics only. No long trials of labor have been permitted because we believe the competent obstetrician should be able, with the aids at hand, to make a decision without long delay. All patients in whom section is considered are x-rayed and receive the necessary pelvimetry. I favor stereoscopic pictures and want as much detail as possible, so that abnormalities of the infant as well as pelvic incompatibility might be discovered. The classical method has been chosen because of the speed and ease with which the operation is carried to conclusion.

*Incidence.*—The 510 cases presented are from a total of 21,759 deliveries, or an incidence of 2.3 per cent. The maternal deaths, and these will be discussed more fully later, were six, or a mortality of 1.1 per cent. Of the infants, where live babies were anticipated, twelve died while the mother was resident in the hospital. There were 11 stillborn infants, all diagnosed before operation. The death rate, therefore, is 2.4 per cent. The weights of the children varied from 5 pounds, 1 ounce, to 12 pounds, 9 ounces.

The age incidence ranged from 13 to 47. Curiously, in the youngest of the patients the pelvic disproportion was at its worst. The condition, in one patient, was accompanied by congenital dislocation of both hips, in another, by severe bone tuberculosis, and, in the third patient, by congenital heart disease. We have always been skeptical of accepting congenital heart disease as a legitimate reason for cesarean section, particularly if the patient had grown to adult life with no sign of cardiac difficulty, but, after seeing such an apparently well patient suddenly develop a decompensation, a revision of opinion became necessary. In two patients, both primiparas, one at 44 and one at 47 years of age, with pelvic measurements on the borderline and x-ray showing well-calcified fetuses, section was performed, despite the feeling that, had the patients been younger, tests of labor might have been tolerated. By far the greater number of sections, as would be expected were in the 20 to 30 year bracket.

Some of the sections reported in the list were performed with sterilization at the request of various medical specialists and not primarily as an obstetric problem.

*Sterilization.*—We sterilize by removing approximately an inch of each tube, obliterating at the cornu of the uterus with continuous catgut on an intestinal needle and folding the distal end of the tube under the broad ligament. While never assuring the patient of a positive sterilization, only one patient has ever reported a pregnancy and, unfortunately, she miscarried at the end

\*Presented at the regular meeting of the Obstetrical and Gynecological Society of Pittsburgh on Feb. 2, 1948.

of the second month, so that the fault was not ascertained. In the repeat sections, where a previous sterilization was supposedly carried out in other clinics and failed, and this was true in six cases, we found the round ligament had been identified as the tube in three cases, and, in two others, the tube had been apparently so buried in adhesions that its structure had not been identified sufficiently for obliteration. In the sixth case, bilateral salpingectomy had been performed by an excellent gynecologic surgeon. At section, the right ovary was found directly adherent over the uterine cornu. We feel that every woman should be offered sterilization at the repeat section if she has one child living and well and the child at current section is apparently healthy and normal. This may appear too conservative but it seems reasonable, that, with the possible difficulties that may arise, it is hardly fair to ask a mother to assume any further risk voluntarily.

CAUSES FOR SECTION	NO.	PER CENT
Placenta previa	52	10.1
Separated placenta	24	4.7
Previous section	121	23.7
Cephalopelvic disproportion	112	21.1
Contracted pelvis	77	15.1
Breech	5	.98
Prolapse of cord	3	.39
Elderly primipara	5	.98
Rheumatic heart disease	45	8.8
Multiple sclerosis	2	.39
Pernicious anemia	1	.19
Psychosis	3	.59
Diabetics	16	3.1
Chronic nephritics	8	1.6
Pulmonary tuberculosis	18	3.5
Fibroids	5	.98
Rupture	3	.59
Gynecologic operations	10	1.9

## STERILIZATION

Multiparity	118
Heart conditions	33
Tuberculosis	18
Psychosis	3
Nephritics	8
Gynecologic operations	10
Diabetics	14

*Anesthetics.*—We are inclined to use nitrous-oxide-oxygen-ether sequence because it definitely contributes to the speed and ease of operation and to the more satisfactory postoperative recovery. To be sure, an anesthetic must be selected for the particular patient, but it goes without saying that no patient's life should be in jeopardy by reason of an anesthetic agent per se. The patient's need is to be evaluated and the anesthetic selected on that basis. The novelty of the anesthesia or the ease of the operating surgeon is decidedly a minor point, the safety of the patient is always the primary consideration.

N <sub>2</sub> O-O-Ether	402
Spinal	9
Open Ether	61
Local	14
Vinethene	2
Pentothal	5
Avertin	7



In preparation of the patient, previous to the appearance of Demerol, we avoided the use of morphia altogether except where local anesthetic was to be used, because it seemed to affect the infant. At the present time, the patient is given 150 mg. Demerol and 1/150 grain hyoscin, 30 minutes before operation, and we have thus far had no difficulty in resuscitation. There was not much in the way of anesthetic difficulty in the less common types. In one of the spinal anesthetic patients, the blood pressure dropped alarmingly for a short time. In one of the Pentothal, the patient stopped breathing on the table and the section was halted until respiration was again instituted. A curious thing happened in one of the Avertin patients. She was a good-sized patient and had a severe mitral lesion. She had been given 1/4 grain morphine before operation and 2/3 of the dose of Avertin per body weight. She did not become conscious until ninety-two hours after operation and seemed none the worse for the experience; indeed, the enforced rest had apparently aided the heart condition.

**Morbidity.**—Using the set rule of considering any patient morbid who had a temperature of 100.4° F. two days consecutively or more, the patients were divided as follows: 110 patients, or 21.5 per cent, were morbid at some time postoperatively. Twelve patients had temperatures up to 105.2° F.

These twelve had the following complications:

1 Phlebitis	6 Abscess in the wound
1 Emboli	4 Pyelitis

Five of these patients had marked distention requiring stomach washing or the use of Wangenstein apparatus. In two patients the question of obstruction became a problem. After careful evaluation, 11½ oz. of castor oil was introduced in the Wangenstein tube and the difficulty disappeared. With distention and vomiting, the decision requires attention to details and then courage. Since Demerol has been available, we use as much as 100 mg. every three hours for the first twenty-four hours after section and try to get patient on full diet by the third day. All patients are given pectoroclysis of 5 per cent glucose until taking fluids freely by mouth and we feel that our patients are more comfortable now than previously by also omitting any postpartum pituitary extract with the exception of the initial dose.

#### *Fetal Deaths.*—

5 Abnormality	3 Melena neonatorum
2 Prematurity	2 Atelectasis

Total of twelve in all . . . 2.4 per cent, 3 diagnosed before operation.

#### *Maternal Deaths.*—

1. Pneumonia. Entered hospital with lobar pneumonia of two days. This patient was a primipara, 19 years of age. She had a contracted pelvis, her membranes ruptured, and the medical consultant decided the operation would have to be risked -----1
2. Diabetic. Noncooperative. Had been in coma at sixth month and again late in seventh month -----1
3. Died of massive pulmonary embolism on the 2nd and 4th days, respectively. Both died within a few minutes after the sudden onset. Both these patients were primiparas of 22 and 27 years respectively. Both were in the eighth month and both had central placenta previa -----2
4. Peritonitis on the fifth day. In this patient, the referring doctor had reported no examination but rectal. On entrance, patient had ruptured membranes with about three-finger dilatation. At operation, the baby showed forceps marks, plainly indicating that an honest history had not been given -----1

There was a total of five deaths out of 510 or a percentage of 0.98 per cent. These were all before the use of the sulfonamides or penicillin.

*Transfusion.*—All placenta previa and all separated placenta patients were transfused. If the patient was not in good condition, the transfusion would be given before operation and repeated when necessary. When in doubt, we feel transfusion is good judgment. Unless hematocrit and specific gravity readings are easily available, one is never able to evaluate the loss of blood or the effect of operation combined with the previous loss of blood. Transfusion is of value, using blood pressure and pulse as a check on the amount used. In transfusion, of course, it goes without comment that the blood pictures must be compatible and that careful cross agglutination should be employed.

*Ruptures.*—Three patients had gone into labor and during the time of getting to the operating room the old scar had ruptured. At operation, three other cases showed a beginning rupture through the old scar and in seven others the scar was so thin that we were amazed they had not ruptured. Of these, two were of the low cervical variety.

### Comments

1. Each case should be evaluated, and, even when there seems reasonable doubt, an x-ray will always guard against a possible abnormality.

2. The previous morbidity of patient, type of repair, or time interval seemed to have nothing to do with the type of scar.

3. In 41 repeat cesareans, where the operation was for disproportion, the succeeding babies weighed from 4 ounces to 2 pounds, 7 ounces more than the previous ones had. The heads had to be displaced out of the pelvis.

4. In 49 cases of repeat cesarean, the placenta was directly under the previous scar.

5. One patient went to full term with a tubal pregnancy and delivered a baby weighing 8½ lbs.

6. One patient developed an obstruction due to a loop of small intestine becoming attached to a bleeding point at the left cornu.

7. One psychosis patient ripped her wound open twelve hours after operation and pulled out her intestines yet recovered without incident.

8. One diabetic went into shock three times within the first forty-two hours and recovered without incident.

9. One patient, a primipara of 35 years, had a cerebral accident when in her second month. This is an extremely rare occurrence in pregnancy and particularly so with recovery of the patient. There was no apparent connection with the pregnancy as far as cause and effect were concerned. The condition was diagnosed as probable congenital aneurysm of the cerebral vessel. Cesarean was decided upon to avoid the strain of labor, with its attendant possibility of a second accident. The patient has made a sustained recovery but apparently is going to have some permanent paralysis of the left leg and left arm. The facial paralysis has almost disappeared.

10. Adhesions did not play a large role but the impression was that we were inclined to find more where there had been previous extraperitoneal sections.

### Conclusions

Five hundred and ten cases of low classical cesarean section have been presented, an incidence of 2.3 per cent. A maternal death rate of 0.98 per cent and a fetal death rate of 2.4 per cent.

119 SOUTH HIGHLAND AVENUE

## THE OVARIAN HYPEREMIA REACTION: ITS USE IN QUALITATIVE AND QUANTITATIVE TESTS FOR URINARY CHORIONIC GONADOTROPIN

E. W. BEHNKEN, B.A., C. W. LLOYD, M.D., AND E. C. HUGHES, M.D.,  
SYRACUSE, N. Y.

(From the Department of Obstetrics, Syracuse University Medical College)

**A**N ACCURATE method for testing for chorionic gonadotropin in the urine, using the ovarian hyperemia in the immature rat as the end point, was first reported by Reiprich<sup>1</sup> in 1933. Since that time, many other authors have reported a similar high degree of accuracy.<sup>2-8</sup> Several workers have been unable to obtain a dependable accuracy with this method.<sup>9, 10</sup>

The purpose of this report is to summarize our experience using this test. The method in use is modified in a few details from that employed in the laboratory of Dr. Emmanuel Klempner.<sup>11</sup> Also included are some results of a dilution procedure which permits use of the hyperemia effect as a means of estimating quantitatively gonadotropin excretion.

### Methods

**Qualitative Test.**—Immature female white rats of the Wistar strain, weighing between 30 and 60 Gm., are used. The animals are kept at between 72 and 76° F. Two of these animals are injected subcutaneously each with 5 c.c. of concentrated morning urine, refrigerated until the moment of injection. The rats are killed with illuminating gas twenty-four hours after injection. This is not essential, but the carbon monoxide of the gas accentuates the hyperemia and makes the color reaction easier to evaluate. The ovaries, with a portion of the uterus and of their mesentery, are dissected free. Sufficient tissue must be left around the ovary to prevent drainage of the blood from the ovarian plexus, with subsequent blanching of the ovary. Excessive intraperitoneal bleeding should be avoided, since staining of the ovary with blood may be misleading. After gentle blotting of the ovary on moist gauze, the color is observed.

The amount of color of the ovary is the basis for the reading of the test. The color is best evaluated in daylight. The finding of one ovary of the two pairs which is bright red, i.e., as red as the kidney, is sufficient for a diagnosis of "positive." The presence of four pale white ovaries is interpreted as a "negative" test. When one or more of the ovaries is reddened to an extent more than will allow a diagnosis of "negative," but still is not as red as kidney, the test is reported as "equivocal."

In instances where a definite diagnosis cannot be made, for example, when the urine is toxic to both of the test animals, when one of the animals dies and the other animal is read as "negative" or "equivocal," or when the reading of the test is "equivocal," it has been found convenient and timesaving to request submission of another urine specimen for testing. Repetition with the same specimen usually gives a result similar to that obtained on the first test. Occasionally, detoxification of the urine with ether is necessary when another specimen cannot be obtained, but the detoxification is undependable and frequently is not effective. When a "negative" response is obtained in animals which appear moribund following injection of urine, the test is repeated. Toxicity is, in almost all cases, due to bacterial contamination of the urine.



**Quantitative Test.**—Serial dilutions of a twenty-four-hour urine collection are given to pairs of rats. The reading of the test is carried out in the same manner as for the qualitative procedure. One "hyperemia unit" has been arbitrarily defined as the amount of material required to cause a definite "positive" response. This is equivalent to approximately three I.U. of chorionic gonadotropin.

### Results

**Qualitative Test.**—The results of the first 703 tests, performed on specimens submitted by 595 patients, have been analyzed. For the total of 703 tests, 603 diagnoses were made. Three hundred and twenty-six tests (54 per cent) were reported as "positive"; 277 (46 per cent) tests were reported as "negative." There were 8 (1.3 per cent) erroneous diagnoses, of which 5 were falsely called "negative"; 3 were called "positive" when the specimens were submitted by patients who were not actually pregnant. The diagnosis was correct in 98.7 per cent of the tests. Of the total of 703 tests, 100 (14 per cent) tests did not provide a diagnosis. Fifty (7 per cent) were repeated because the urine specimen was toxic to the animals. Fifty (7 per cent) of the tests were reported as "equivocal." Repeated tests on the urines of the patients having "equivocal" tests resulted in a diagnosis of "positive" in 21 (42 per cent) and a diagnosis of "negative" in 20 (42 per cent). Seven (14 per cent) of the patients aborted before another specimen for testing could be obtained and 2 (4 per cent) had normal menstrual periods.

Of the eight erroneous results found in this analysis of 703 tests, five consisted of a reading of "negative" for the test on specimens submitted by patients who subsequently were found to have normal pregnancies, and three consisted of readings of "positive" for specimens from nonpregnant patients. Two of the erroneous "negative" tests may have resulted from the submission of specimens too early in pregnancy, since they were submitted at about the time of the first missed period. A third erroneous "negative" test was compared with the Friedman and the standard Aschheim-Zondek test, each of which was also read as "negative." It is felt that two of the erroneous "positive" tests may have been due to inexperience, since these errors occurred soon after this method of testing for chorionic gonadotropin was instituted in our laboratory. The record of each of these tests shows that the reaction was a "light red." In view of subsequent experience, reactions of this sort are now called "equivocal," and the test is repeated. In two tests performed after the statistics reported above were compiled, erroneous diagnoses of "positive" were made on urine specimens from patients found at operation to have corpus luteum cysts. Zondek, Sulman, and Black<sup>4</sup> have also reported a false "positive" test in a patient with a corpus luteum cyst.

The accuracy of almost 99 per cent reported here is at variance with the accuracy reported by some other laboratories. There are three factors which may account in part for this discrepancy: (1) A greater volume of urine is used for injection than in other laboratories which have reported poor accuracy; (2) our animals are sacrificed twenty-four hours after injection, which tends to cause a more dependable ovarian reaction than the shorter tests<sup>4, 7</sup>; (3) a definite diagnosis is not made in any case where a reaction greater than "negative" or less marked than a full "positive" is found. Since approximately 50 per cent of the patients having "equivocal" tests later develop "positive" tests, and 50 per cent develop "negative" tests, it is obvious that an arbitrary grouping of these "equivocal" tests into the "negative" group, such as was done by Bunde,<sup>10</sup> introduces a considerable error.

The unpredictability of this method of testing for chorionic gonadotropin which was reported by Farris<sup>9</sup> is overcome in part by the factors listed above.

This author reports a very high incidence of false "positive" tests. Urinary gonadotropin of the nonpregnant individual causes a hyperemic effect reaching its greatest intensity in a few hours and tending to fade by 24 hours.<sup>12</sup> Chorionic gonadotropin causes an intense hyperemia at 24 hours which is certainly as intense and possibly more intense than that seen at two or six hours. The response caused by the injection of urine containing gonadotropin of the nonpregnant person has not, in our hands, been nearly as intense as that caused by the injection of urine containing chorionic gonadotropin. Therefore, we feel that the interval of twenty-four hours between injection and interpretation and the requirement of sufficient hyperemia to cause a color as red as the kidney for the test to be called "positive" eliminate many erroneous reports of "positive."

All the causes of the so-called "equivocal" reaction have not been discovered, but a few conclusions can probably be drawn. A considerably higher percentage of spontaneous abortions occurs in patients whose urine yields an "equivocal" result than occurs in the patients whose urines yield "positive" reactions. This increase in abortions—21 per cent following an "equivocal" reaction as contrasted with 8 per cent following a "positive" reaction—is probably significant, although it must be realized that absolute accuracy in follow-up records is not possible. It would seem possible that these patients are excreting a smaller amount of chorionic gonadotropin than is excreted by the patient with a normal pregnancy.

Several of the patients whose urines caused "equivocal" reactions and whose second urine specimen submitted a few days later caused a "negative" reaction may have been near the time of ovulation, since an apparently normal menstrual period occurred a little over two weeks after the date of submission of the first specimen.

The insensitive animal may also cause an "equivocal" reaction. Not infrequently one of the two rats has only a weak response, whereas the second animal of the pair has a strongly "positive" reaction. Our animals are kept between 72 and 76° F. at all times, since it has been found that increased temperature definitely decreases the responsiveness to gonadotropins. If the urine is toxic but not actually lethal to test animals, the sick animal does not have normal sensitivity to gonadotropins. If a "negative" response occurs in sick animals, the test is repeated.

**Quantitative Test.**—The excretion of gonadotropin throughout normal pregnancy has been determined by study of 14 patients. A rapid increase in daily excretion rate occurs during the first few weeks of pregnancy until a peak of about 12,000 or more rat hyperemia units per 24 hours is reached at about the 60th day. A fairly rapid decline then occurs until a relatively low rate of excretion at between 1000 and 4000 rat hyperemia units per 24 hours is reached at about the end of the first trimester. Excretion at this level is maintained throughout the last two trimesters of pregnancies. This is in agreement with the findings of Browne and Venning<sup>13</sup> and Evans et al.<sup>14</sup>

In seven patients, the presence of a threatened abortion was suspected. Levels of gonadotropin excreted were 50 per cent to 75 per cent lower than are found in normal pregnancy of the same duration. As the abortion became inevitable, the rate of excretion rapidly declined. Death of all chorionic tissue was suspected when no gonadotropin was present in the urine. Abortion subsequently occurred in all seven patients. A lowered rate of excretion in patients with threatened abortion has been reported by other authors.<sup>11, 13</sup> It is our belief that therapy is justified as long as the finding of chorionic gonadotropin in the urine indicates the presence of viable chorionic tissue. A falling level of excretion indicates the need for increasing the vigor of treatment. The absence of gonadotropin in the urine is an indication for stopping therapy. We are of

the opinion that following patients in this manner eliminates much useless therapy.

Two of the patients whose gonadotropin excretion was studied throughout pregnancy developed definite, though not severe, symptoms and signs of pre-eclampsia. In both of these patients, a definite increase in gonadotropin excretion occurred several weeks before any other objective signs developed. In one of these patients, a diabetic, the level of excretion was as high as 15,000 rat hyperemia units per 24 hours during the eighth month when the normal excretion is not over 4,000 units. In the other patient, an excretion of 6,000 units per 24 hours was maintained for several weeks before the onset of symptoms of toxemia. A patient with severe toxemia, whose condition necessitated interruption of pregnancy, excreted over 12,000 rat hyperemia units per 24 hours. Two other patients with severe pre-eclampsia also had high titers averaging 12,000 units per day. Gonadotropin excretion was normal in another patient who developed edema and was suspected of having pre-eclamptic toxemia. The edema cleared completely without development of any other signs of toxemia following a few days of bed rest, fluid restriction, and low-salt diet. A patient with chronic nephritis and hypertension had a normal rate of excretion.

The elevation in gonadotropin levels in patients with pre-eclampsia or eclampsia, as reported by Smith and Smith,<sup>15, 16, 17</sup> can be easily recognized. We have, as yet, no explanation for our finding of an increased excretion in the urine before the appearance of signs of toxemia when these authors could detect this rise only in the serum and not in the urine until the toxemia became evident.

Excretion of gonadotropin by a patient with a chorionepithelioma with metastasis, the diagnosis of which was confirmed by the finding of chorionic gonadotropin in fairly large amounts a month after delivery, reached levels of over 16,000 rat hyperemia units before death. Tumor tissue removed at autopsy contained a high concentration of gonadotropin. The high level of gonadotropin excreted by this patient is in complete agreement with many previous reports in the literature.<sup>4</sup>

In three brief case reports—two of patients with hydatidiform moles and one of a patient with a chorionepithelioma—Zondek et al.<sup>4</sup> mention the estimation of the amount of the ovarian hyperemia-producing factor in the urine. No details of procedure are included. The values reported by these authors are much higher than the values found in any of our studies. It is possible that this difference may be due, in part, to a difference in animal sensitivity, but it is most probable that a difference in end point is the most important factor. For the sake of uniformity, we have set up our end points as a definite bright red. Many times, a less intense reddening of the ovary occurs in animals which have received higher dilutions, indicating that some gonadotrophic effect undoubtedly has occurred. It has been our impression that this slight reddening is too indefinite and unpredictable to be a useful end point.

The value of this method of quantitatively estimating chorionic gonadotropin is its simplicity, and we feel that it has sufficient accuracy to have clinical usefulness. Expense to the patient is low enough so that consecutive determinations can be frequently performed. Although absolute values are not comparable, the patterns of excretion are similar to those obtained with other methods.

### Summary

1. In 703 qualitative tests performed on urine for the presence of chorionic gonadotropin, a definite diagnosis was made in 603 instances. Of the 603 diagnoses made, 595 (98.7 per cent) were correct.

2. Of the 100 tests for which no diagnosis was made, 50 were reported as "equivocal" and tested again later; 50 were repeated because the urine specimen was toxic to the animals.

3. Of the 50 tests reported as "equivocal," 28 (56 per cent) were submitted by patients who were later found to have been pregnant. Twenty-two (44 per cent) were from patients who were later found not to have been pregnant. The incidence of abortion was 21 per cent in the patients who submitted a specimen reported as "equivocal," whereas only 8 per cent of the patients having a test reported as "positive" subsequently aborted.

4. By a simple procedure involving serial dilutions, a roughly quantitative estimation of gonadotropin excretion can be made.

5. During normal pregnancy, a high peak of gonadotropin excretion is reached during the first trimester, with a decline of excretion to a relatively low level by the end of the third month. This low level is continued throughout the last months of pregnancy.

6. In threatened abortion, the excretion of gonadotropin is lower than for the normal patient at a comparable stage of pregnancy. A rapidly falling rate of excretion is an indication for more vigorous therapy. Death of chorionic tissue should be suspected in the absence of gonadotropin in the urine.

7. A high gonadotropin excretion late in pregnancy may be associated with toxemia.

8. A patient suffering from a chorionepithelioma with metastasis had a very high excretion of gonadotropin before death.

### References

1. Reiprich, W.: *Klin. Wchnschr.* 12: 1441, 1933.
2. Kelso, R. E.: *Am. J. Clin. Path.* 10: 293, 1940.
3. Frank, R. T., and Berman, R. L.: *AM. J. OBST. & GYNEC.* 42: 492, 1941.
4. Zondek, B., Sulman, F., and Black, R.: *J. A. M. A.* 128: 939, 1945.
5. Zondek, B., and Sulman, F.: *J. Clin. Endocrinol.* 7: 159, 1947.
6. Kaminester, S.: *AM. J. OBST. & GYNEC.* 47: 265, 1944.
7. Salmon, U. J., Geist, S. H., Salmon, A. H., and Frank, I. L.: *J. Clin. Endocrinol.* 2: 167, 1942.
8. Kupperman, H. S., Greenblatt, R. B., and Noback, C. R.: *J. Clin. Endocrinol.* 3: 548, 1943.
9. Farris, E. J.: *AM. J. OBST. & GYNEC.* 48: 200, 1944.
10. Bunde, C. A.: *AM. J. OBST. & GYNEC.* 53: 317, 1947.
11. Klempner, Emmanuel: Personal communication.
12. Farris, E. J.: *AM. J. OBST. & GYNEC.* 52: 14, 1946.
13. Browne, J. S. L., and Venning, E. M.: *Lancet* 2: 1507, 1936.
14. Evans, H. M., Kohls, C. L., Wonder, O. H.: *J. A. M. A.* 108: 287, 1937.
15. Smith, G. V., and Smith, O. W.: *Proc. Soc. Exper. Biol. & Med.* 30: 918, 1933.
16. Smith, G. V., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 33: 365, 1937.
17. Smith, G. V., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 38: 618, 1939.
18. Schnoeneck, F. J.: *AM. J. OBST. & GYNEC.* 39: 485, 1940.



## A TECHNIQUE FOR RE-ESTABLISHING TUBAL PATENCY\*

CLAYTON T. BEECHAM, M.D., F.A.C.S., AND MURRAY D. SIGMAN, M.D.,  
PHILADELPHIA, PA.

*(From the Department of Obstetrics and Gynecology, Temple University Hospital)*

IT WOULD be a tremendous task, indeed, to describe all the operations that have been devised for the correction of tubal occlusion. Many operations for this cause of infertility have been forgotten. There are several worth-while operative procedures, however, that have been fruitful and should not be abandoned. The technique to be described involves old surgical principles with the addition of one adjunct, i. e., sulfanilamide.

In 1942 Beecham and Friday,<sup>1</sup> in a report on the local tissue reaction to sulfanilamide established that: First, the only harmful effect from sulfanilamide application locally in the abdominal wall, pelvic, or abdominal cavity occurred where the crystals are used in fatty tissue. When sulfanilamide crystals came in contact with fatty tissue that had been disturbed there was a resulting necrosis and a typical foreign-body response. Second, locally, sulfanilamide had a distinct styptic action. Third, experimentally, local sulfanilamide implantation caused a reduction of postoperative adhesions. With these results in mind, one of us (C. T. B.) has used sulfanilamide crystals in the pelvis almost routinely since 1941. The aforementioned conclusion from experimental work in animals have been borne out in everyday operative work. Falk and Blinick<sup>2</sup> speak of using sulfanilamide crystals to "minimize the possibilities of postoperative intestinal adhesions." As far as we know, this is the only outside confirmation of the observation on a lowered incidence of adhesions following sulfanilamide over the peritoneal operative site.

The applicability of local sulfanilamide in the treatment of tubal occlusion was revealed to us in the following manner:

Miss B. B., aged 19 years, was operated upon by C. T. B. at Temple University Hospital Dec. 4, 1942. At that time, a tubovarian abscess about 9 cm. in diameter was removed on the right side. The left tube and ovary were bound down in the cul-de-sac. The tube was three times its normal diameter, being moderately thickened. The fimbria were closed and the entire structure closely adherent to the ovary. The picture was one of chronic or recurrent gonorrhea. A salpingolysis was done. The fimbriated end of the remaining tube was cut open preserving the fimbria and a probe passed to the uterine cornu. Sulfanilamide crystals were then poured into the tubal lumen. Five Gm. of crystals were used in and around the tube.

The patient married shortly thereafter, conceived, and was delivered, twenty-one months after the operation, of a full-term, normal fetus.

The reason we had tried the above technique in the operating room was simply to attempt some rational conservative procedure in a young girl. We had hoped only to salvage the adnexa, not thinking that the patient could ever conceive. The surprising result led us to employ the intratubal sulfanilamide

\*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 4, 1947.

crystals further as an easy conservative surgical procedure in pelvic inflammatory disease and for asymptomatic tubal block in sterility cases.

### Application

The procedure is employed in two types of cases. First, those who have had complete infertility studies and in whom tubal occlusion was the most important factor. Roentgen evidence is often sought to demonstrate the point of occlusion although we do not make a routine practice of this procedure. (Fig. 1.) None of our cases have revealed an occlusion at the isthmus nor have we encountered in this small series salpingitis isthmica nodosa. From our observation it would seem that the vast majority of old salpingitis cases are blocked at the fimbria.

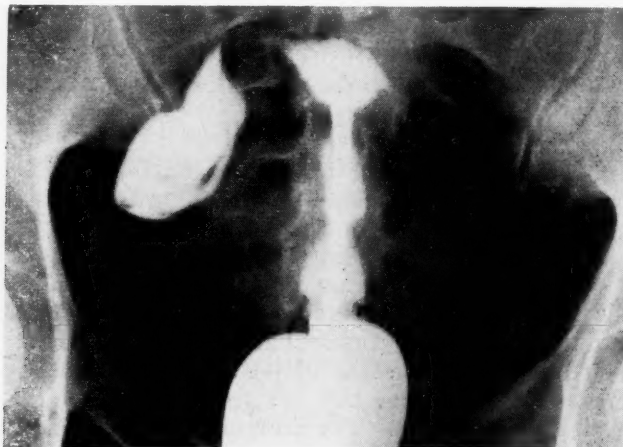


Fig. 1.—Typical view of tubal occlusion at the fimbria.

The second group of cases where the operation was employed was in chronic or recurrent gonorrhea. The chief complaint in these individuals was chronic pain and/or menometrorrhagia. The adnexa were fixed by adhesions, thickened, fimbria occluded, and often the uterus fixed in retroversion. We were operating here for relief of symptoms and not to cure infertility.

### Technique

This procedure has not been materially altered since the original case. It is often necessary to do a lysis of adhesions to uncover the pelvic viscera. The uterus and adnexa are freed from the adhesive bed again by sharp dissection. The tubes are next freed from all but their natural attachments. The closed fimbria are grasped with Babcock visceral clamps and held by slight tension while a careful stab incision is made in what appears to be the ostium. This opening is gently enlarged with a long Kelly hemostat acting as a dilator, if the tube is not already dilated. A blunt probe is passed down to the isthmus and this is almost always possible if a proper salpingolysis has been done. Holding the tubal lumen open with a long tissue forceps, sulfanilamide crystals are poured into the tube and the excess up to 5 Gm. allowed to fall into the pelvic cavity. (Fig. 2.) A suspension is done if the uterus is retroverted. The abdomen is closed without drainage and a Rubin test is done two weeks following operation.

### Results

Eight patients have been subjected to operation for infertility due to tubal block. Of these eight, two have conceived and delivered at term for a 25 per cent successful result. Seven of the eight have consistently demonstrated patent tubes at a normal pressure. In one of the eight, the tubes have remained closed. Only one complication was noted in this group of eight patients and that was a flare-up of an old gonorrheal inflammatory disease. This patient needed a colpotomy three weeks after operation but since then has demonstrated tubal patency at 60 mm. of mercury.

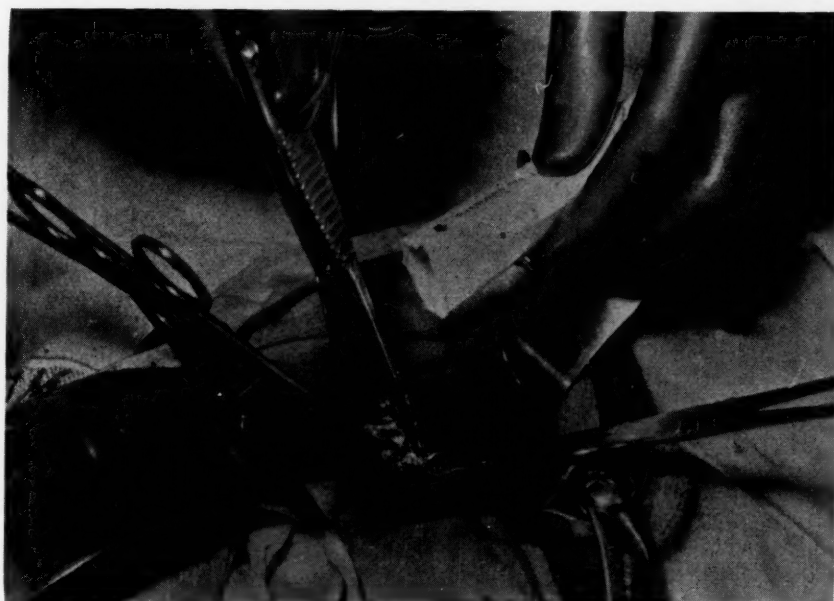


Fig. 2.—Fimbria held with visceral forceps, long tissue forceps in the tubal lumen, and sulfanilamide crystals being introduced.

A second group subjected to this operation consisted of ten patients with adnexal pathology, for the most part gonorrheal in nature. These patients all had pelvic pain that was incapacitating enough to warrant surgery. Three of the ten had tubovarian endometriosis with tubal block. Of these ten operated upon, two have conceived, one delivered at term, and one aborted. Three of the ten patients have closed tubes in spite of being asymptomatic, while one has been lost sight of and we have no follow-up. One of the ten had a mild flare-up of the pelvic inflammatory disease. She is symptom free now and her tubes are open.

In those operated upon primarily for infertility we have had a 25 per cent success. In those operated upon for pelvic symptoms and not to relieve infertility, we have obtained a 20 per cent success as far as conception goes, although one of these cases aborted spontaneously at two months. There were no ectopic pregnancies encountered in the group.

### Discussion

From a review of the literature, it is quite evident that tubal occlusion at the fimbriated end offers the greatest chance of success in plastic surgery. Results in the past have not been good and consequently the operation is all too

often condemned today. In general, one may gather from the works of Solomons,<sup>3</sup> Greenhill,<sup>4</sup> Lovset,<sup>5</sup> Lastra and Jakob,<sup>6</sup> and Siegler<sup>7</sup> that the average success is approximately 10 per cent. Salpingolysis has been successful in approximately 10 per cent of cases when employed although Siegler reports a 17 per cent success. Tubal patency following this operation of salpingolysis and sulfanilamide application is comparable to the figure found in a series by Sovak,<sup>8</sup> where conception results were not given.

It would seem from this series that salpingolysis is the operation of choice, with the added step of sulfanilamide crystal implantation. The salvage rate is higher than in other series of comparable operations.

In addition, this technique seems applicable to the old chronic pelvic inflammatory lesion where we have long-standing pathology in young women and we have no desire to sacrifice the adnexa.

### References

1. Beecham, C. T., and Friday, R.: *AM. J. OBST. & GYNEC.* 44: 88, 1942.
2. Falk, H. C., and Blinick, G.: *AM. J. OBST. & GYNEC.* 54: 314, 1947.
3. Solomons, B.: *J. Obst. & Gynaec. Brit. Emp.* 43: 619, 1936.
4. Greenhill, J. P.: *J. A. M. A.* 33: 35, 1937.
5. Lovset, J.: *Acta obst. et gynec. Scandinav.* 20: 344, 1940.
6. Lastra, E. T., and Jakob, A.: *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 327, 1942.
7. Siegler, S. L.: *Fertility in Women*, Philadelphia, 1944, J. B. Lippincott Company.
8. Sovak, F. W.: *Am. J. Surg.* 33: 406, 1936.

### Discussion

DR. NEWLIN PAXSON.—This interesting paper presents a new idea based on sulfanilamide application, which may be useful in destroying adhesions within the abdomen. It is based on their original work published in 1942. The high incidence of pregnancy that one would not normally expect following surgical procedures, and the second inference, that of absence of ectopic pregnancy, would suggest the restoration of tubal patency. Although the group is too small to draw final conclusions the results are interesting. It would be well for all of us who do plastic operations on tubes to use sulfanilamide and send our results to Dr. Beecham so that he could collect a large enough series to assemble statistics. As soon as a study of this type is reported, it would be well to have hysterosalpingography before and after operation because its success could be proved in that way.

DR. SIGMAN (Closing).—Our method has been a conservative approach to this subject and that, of course, is what we always want in pelvic surgery. The operations and surgical approaches to tubal blockage and infertility as a whole have been very discouraging. Most recent reports that I could discover in the literature have ended up with a very discouraging report that the surgical approach is unsatisfactory. Yet I think all of us must consider one fact, and that is that there are a certain group of patients who will continue to come in search of alleviation of sterility.

There was only one other interesting piece of work in re-establishing tubal patency by pharmacosurgical methods being done by a group in Stockholm. Penicillin was inserted in the tube and followed later by injecting penicillin retrograde into the tubes every 12 hours. They have reported an occasional successful case; they do not yet have a series of cases. The second method by the same group is, at laparotomy after tubal patency is secured, to place cholesterol wax in the tube and close the abdomen. After operation, a vaccine is given to raise the body temperature to 104° F., melting the wax, which absorbs, and leaves the tubes patent. This too is still in the experimental stage. I feel that our method, inserting sulfanilamide powder into the tubal lumen, is a conservative approach and offers good results.



## IN DEFENSE OF THE UTERINE INTERPOSITION OPERATION

LEO BRADY, M.D., BALTIMORE, MD.

*(From the Gynecologic Department of the Johns Hopkins Hospital and University)*

THREE previous reports from the gynecologic department of the Johns Hopkins Hospital, published in 1922, 1926, and 1935, have dealt with the results obtained by the staff with the Watkins' interposition operation in the treatment of uterine prolapse. This fourth report is a further study and critical evaluation of the results of this operation since 1930 and is prompted by the author's conviction that the operation has an important place among gynecologic procedures. It is not to be inferred that it should always be carried out in the surgical correction of uterine prolapse. There are more vaginal hysterectomies, Manchester, Spaulding-Richardson composite operations than interposition operations performed in the Johns Hopkins Hospital at the present time. Indeed, the name of one member of the staff, Edward H. Richardson, is associated with the development of the composite operation. His reports and those of Telinde have emphasized the good results obtainable with this procedure.

Our experience with the interposition operation during the past seventeen years suggests that its recent marked loss in popularity is unwarranted and that many criticisms of it are unjust. For example, when one reads of a pregnant woman whose uterus has been interposed under the bladder, having difficulty with delivery, it is not the operation, but the operator who should receive the criticism. There is never any excuse for performing an interposition on a woman in the child-bearing age and leaving her with the possibility of becoming pregnant.

Some of the critics of the operation point out that uterine cancer may still develop postoperatively at any time. This is true, but as there is no record of its occurring in a single case operated on at the Johns Hopkins Hospital, its incidence must be low. One must remember that a malignancy reported developing as early as twelve or even eighteen months after an interposition operation may have been present and overlooked at the time of the operation. The operation should not be performed on a woman with metrorrhagia unless some benign explanation for the bleeding, such as a cervical polyp, is found and the possibility of malignancy ruled out; nor should the operation be selected for women with excessive menstrual bleeding.

A dilatation of the cervix and curettement of the endometrium should always be the first steps in performing an interposition operation. Whenever an excessive amount of material is obtained or the consistency of the curettings suggests malignancy, the correction of the prolapse should be delayed until a microscopic report is obtained. Although there are in our series a few cases in which the cervix was not amputated and the prolapse still was corrected, the majority of the staff feels that an amputation is an integral part of a properly

performed interposition operation. It helps ensure the permanence of the correction of the prolapse and almost eliminates the possibility of the development of cervical carcinoma in the future.

A few gynecologists claim that interposition of the uterus under the bladder increases the likelihood of urinary complications. While some patients do have difficulty in voiding spontaneously and may need repeated catheterizations, this is equally true of women on whom a vaginal hysterectomy or the composite operation has been carried out. An occasional case of postoperative cystitis develops, but, if recognized promptly and treated with chemotherapy, the infection almost invariably clears up in a few days. There is no record in our series of a permanent bladder disorder being caused by an interposition.

Some members of the staff place indwelling catheters in the bladder for from a few days to over a week. Others prefer repeated catheterizations until the bladder regains its tone. All agree that it is most important to avoid overdistention of the bladder. In recent years, the writer has gotten all of his patients in satisfactory condition out of bed on the second postoperative day, and even on the day of operation, if the patient is unable to void lying down. He has a firm conviction that, by doing so, the need for repeated catheterizations has been reduced.

Before presenting the results of this study of 145 women operated on since 1931, the previous reports on the interposition operation by the gynecologic staff of the Johns Hopkins Hospital will be briefly reviewed. The first of these was by H. N. Shaw, and was based on 118 operations performed between 1900 and 1921. However, only 58 of these patients were traced. This is understandable, as many of the women in the series were of the dispensary class, who frequently changed their residences. Also our social service follow-up was then in its infancy.

During the first two decades of this century, the contraindications to the interposition operation were not appreciated by all operators. For instance, in Shaw's series, 34 women were under forty years of age when operated upon. Moreover, the operation was performed on two women in whom future pregnancy was possible and, incredible as it may seem, one of them did later deliver a ten-pound baby. From about 1915 on, all gynecologists began to realize that the use of the operation should be restricted almost entirely to the treatment of patients near or subsequent to the menopause.

Because of the early lack of awareness of the limitations of the interposition operation, it seems fair, in an attempt to evaluate this surgical procedure, to eliminate from Shaw's series all those patients operated upon prior to 1914. If this is done, we find that Shaw was able to trace 21 of the women operated upon in the Johns Hopkins Hospital between 1915 and 1921. There was only one failure in this group.

The second study was made by the present writer and reported in 1926. It dealt with the results obtained by Dr. T. S. Cullen at the Johns Hopkins Hospital and Church Home Infirmary and with those obtained by the author himself. In all, 56 patients were studied. No patients in this series became pregnant later. There were no postoperative deaths. Two patients had postoperative bleeding from the perineum. This was easily controlled. One developed a chronic cystitis which worried her for several months. Today, chemotherapy would doubtless give prompt relief in a similar case.

Forty-eight of the 56 patients, or 85 per cent, were traced. Forty-five women reported that they were relieved of all their symptoms and a large percentage of these were examined and found to have no evidence of prolapse. Three of the forty-eight felt that the results were not entirely successful, but only one had to have a second operation. She developed a cystocele eleven years after the first operation. In brief, 45 out of the 48 women traced, or 93 per cent, made a complete recovery and were relieved of all their symptoms.

The third report, by Everett, was based on a study of 68 patients. One died of pulmonary embolism. Sixty-seven were discharged as well. Everett was able to get data on the ultimate outcome of 48 of the 67 patients. Forty-six, or 95 per cent, showed excellent anatomic results. In two cases, after five years of complete relief, there was a recurrence of moderate prolapse. Three complained of dyspareunia, but this was due not to the interposition, but to a too snug perineorrhaphy.

This, the fourth report of our results with the interposition operation, is a study of 145 patients operated upon in the past seventeen years. This number includes all patients on whom this operation was performed in the Johns Hopkins Hospital by the gynecologic staff and also some additional private patients operated on by the writer at other Baltimore hospitals.

In 141, the operation was performed for uterine prolapse. The degree of descensus was moderate in 34, marked in 50. There was a complete, or what is sometimes called a third-degree, descensus in 57. In two, there were large cystoceles without any procidentia. In two, the body of the uterus had been previously removed by a supravaginal hysterectomy, and in later years the cervical stump had prolapsed. In these two, the interposition principle was followed, but instead of the uterine body, the cervical stump was interposed under the bladder.

As the great majority of women in this study were beyond the menopause, we find records of only six sterilizations. No patients later became pregnant. Thirty-five women were over 60 years of age. Twenty were over 65, and four over 70, which indicates that age itself was seldom considered a contraindication to this operation. On general physical examination, a systolic blood pressure of over 180 was found in six women. This series also included two diabetics with cases of moderate severity, both of whom had uncomplicated convalescences.

Six patients had enteroceles in addition to the uterine prolapse. Small myomas were present in thirteen uteri. At operation, the myomas were removed at the same time as the interposition operation was carried out. Only when the patient is at or beyond the menopause and the tumors small is this recommended. Under other conditions a vaginal hysterectomy is advisable.

The only serious operative accident was the perforation of the bladder in one case. The opening was immediately closed, and the patient had no post-operative difficulty, not even developing a cystitis. In one case, the body of the uterus was traumatized to such extent in being delivered, that a partial fundectomy was added to the interposition operation.

A cervical amputation was carried out in 132 cases. Microscopic study of the removed cervixes showed hyperkeratosis in 18 and squamous metaplasia in 12. Almost all showed infection, the pathologic report varying from slight to marked endocervicitis. In one patient operated upon in 1934, the cervix showed a very early squamous-cell carcinoma. As the patient was 61 and it was felt that the amputation had been sufficiently high to give considerable margin above the malignancy, no further treatment was advised. It has now been 13 years since the operation, and the patient is still enjoying good health at the age of 74.

There were two operative deaths. One woman died on the fourteenth post-operative day and the other on the thirteenth. An autopsy of the first case showed an extensive pulmonary embolus. No autopsy was obtained on the



second, a 67-year-old woman, but she was carefully studied by the medical department postoperatively, and a diagnosis of coronary thrombosis was made. This second fatality might have occurred even if there had been no operation.

The nonfatal postoperative complications consisted of 13 infections of the bladder, all of which cleared up under chemotherapy, and of two instances of thrombophlebitis. Fortunately, the two latter were mild in character and were giving the patients very little discomfort when they were discharged from the hospital. In only one patient did any postoperative bleeding occur, and this was not profuse. It came from the anterior vaginal wall and was easily controlled.

Of the 143 women who survived the operation, 115 (80 per cent) were heard from between October 1, 1947 and January 1, 1948. Eighty-four have been examined. The operation completely relieved the symptoms of prolapse, cystocele, or rectocele in 110 of the 115 cases followed (95.6 per cent).

A review of the small percentage of the cases in which there was a partial or complete failure is of importance from the standpoint of bettering future results. One woman, 11 years postoperatively, had a return of the rectocele without any uterine prolapse or cystocele. This was corrected surgically. Another woman, after two years, noticed that she could feel her cervix at the vaginal orifice; but this gave her no discomfort and no further treatment was carried out. The two above-mentioned cases might be classified as partial failures. One patient had a return of the prolapse within a year, and a Le Fort operation was then done. A second woman, 70 years of age when operated upon, replied to a questionnaire sent her four years after she had left the hospital that she was in perfect health, but then wrote again a few months later stating that she had had a severe fall following which the prolapse returned. In a third patient, the interposition operation held for 11 years, but then there was, rather suddenly, a marked return of the prolapse. These three cases are considered complete failures even though in one, relief was obtained for four years, and in another, for eleven years.

Only four of the 113 patients were under forty years of age when operated upon. These figures are a marked contrast to Shaw's report dealing with the patients operated upon during the first part of the century. The four patients in this present series were between 30 and 35 years of age. They have been checked in the past few months and, in all, the uterus is in excellent position. Nevertheless, the author feels that an interposition should not be performed in a woman under forty. All the young women in our present series were operated on over twelve years ago. Today, some other operation for the prolapse would be performed.

A direct question about dyspareunia was asked nearly all the women who were examined. Only two complained of it and in them it was due to a too snug perineorrhaphy. Many of the women we have examined in the past few months are now well advanced in age, so the information obtained about dyspareunia is not entirely reliable.

The average number of years since the interposition operations were performed in the patients whom we have traced is between seven and eight. More than ten years have elapsed since 33 of the women were operated on and more than five years since 88 had the interposition. These figures are strong evidence of the permanency of the correction of uterine prolapse by the operation.

Of the 110 patients on whom the operation was a complete success, four have now died of medical conditions in no way associated with the operation. One died at 76, six years after the interposition. A second died at 70, five years after the surgery; a third died at 69, four years postoperatively, and a fourth at 71, after enjoying 12 years of good health following the operation.

One hundred and eight women are known to be living and well at the present time. Four of these are over eighty years of age, thirteen between 75



and 80, and thirty-four, 70 or over. Many elderly women who have interposition operations live on afterward for many years. It is important to emphasize this. Not infrequently the families of elderly women advise against surgery because, as they say, "Grandmother is not going to live many years anyhow, and so why worry her?" The author has no more grateful patients than these elderly women who have had their uterine prolapse corrected surgically. They seem to take a new lease on life.

Having now presented the results of the interposition operations since 1930, the author believes it would be of interest to add to the figures just given those in the three previous reports from the gynecologic staff, omitting the cases in Shaw's series operated on prior to 1915. Two hundred and ninety operations were performed with three operative deaths. However, one fatality was due to coronary disease, and might have occurred even if the patient had not been operated on. The other two were the result of pulmonary emboli. There is the possibility that by getting patients out of bed on the day of operation or at least on the second postoperative day, the danger of embolus is much decreased. In the past five years, the majority of my gynecologic patients have been out of bed early and, during that time, only one small embolus was observed from which the patient quickly recovered.

Out of the 287 women surviving operation, 232 were traced (80 per cent). Of these, 221 were completely relieved of all their symptoms. This gives a percentage of 95 per cent of complete success with the interposition operation on those patients followed.

The operations on eleven women are classified as failures and make up the 5 per cent of unsuccessful operations. However, one woman has no symptoms and merely has noticed that when she stands she can feel the cervix at the vaginal orifice. Three other women were well for ten years and then had to have a second operation; one for prolapse of the uterus, a second for a cystocele, and a third for a rectocele. Possibly some of these ten cases should not be considered as complete failures. This study indicates the necessity of a long term follow-up of patients operated on for uterine prolapse, since some of the recurrences in the series occurred after as long as ten years.

### Summary

1. Since 1931, uterine interposition operations have been performed on 145 patients at the Johns Hopkins Hospital. The results obtained have been presented.

2. These figures have been combined with the figures cited in three previous reports by the gynecologic staff of the Johns Hopkins Hospital.

3. The results obtained show that the uterine interposition operation is satisfactory for uterine prolapse in women at or beyond the menopause.

4. The author does not claim that the interposition operation is the procedure of choice in all cases of uterine procidentia, but points out that in his hands and in those of the other members of the Johns Hopkins gynecologic staff, it has yielded a high percentage of successes.

### References

1. Brady, L.: Surg., Gynec. & Obst. 43: 476, 1926.
2. Everett, H.: Surg., Gynec. & Obst. 61: 403, 1935.
3. Richardson, E. H.: AM. J. OBST. & GYNEC. 34: 814, 1937.
4. Shaw, H. N.: Surg., Gynec. & Obst. 34: 394, 1922.
5. TeLinde, R., and Richardson, E. H., Jr.: AM. J. OBST. & GYNEC. 45: 29, 1943.
6. Watkins, T. J.: Am. J. Obst. 15: 520, 1899.

## THE LEFORT COLPOCLEISIS: AN ANALYSIS OF 43 OPERATIONS\*

CHARLES MAZER, M.D., AND S. LEON ISRAEL, M.D., PHILADELPHIA, PA.

*(From the Department of Gynecology, Mount Sinai Hospital)*

**P**ROLAPSE of the uterus and the associated descent of the vagina, being the consequences of developmental defects and childbearing trauma, have always engaged attention. Recently it has been emphasized that procidentia may not only give rise to ureteral kinking and secondary hydronephrosis,<sup>1</sup> but may also be the cause of hypertension.<sup>2</sup>

Extensive operations for the correction of uterovaginal prolapse in women who are still in the childbearing age should obviously be avoided. Fortunately, most instances of annoying first- and second-degree prolapse occur after the childbearing age, during the premenopausal, fifth decade of the woman's life. Complete prolapse is most common after 60 years, when postmenopausal genital atrophy has already occurred. Following the accepted trend in gynecology, we avoid abdominal operations and attempt to treat all patients with uterovaginal prolapse by the vaginal route. In the postmenopausal patient, whose state of health demands as little surgical procedure as possible and in whom the coital function is not essential, an almost complete vaginal closure, the so-called LeFort colpocleisis is our operation of choice.

The advantages of the LeFort operation include the rapidity and ease of its performance, even under local anesthesia, factors of inestimable value in avoiding undesirable shock and trauma in elderly women who are unfit for more extensive operations. The principal disadvantage is that in the event of vaginal bleeding there are no means whereby one may determine the cause of the bleeding without abdominal hysterectomy. LeFort's first operation was performed in two stages, the resulting inverted U-shaped channel was sufficient to permit sexual intercourse. Indeed, his first patient was later delivered of a living, almost full-term child, after incision of the previously contrived septum.<sup>3</sup> The first colpocleisis in the United States was performed in 1880 in Boston by Dr. Fanny Berlin.<sup>4</sup> Since then, the operation has been variously modified, especially in regard to the type of lateral channel and the repair of the pelvic floor, and has been evaluated by several gynecologic clinics.<sup>5</sup> It is a relatively simply surgical procedure, one admirably suited to elderly women in whom more extensive operations are contraindicated. It deserves a limited application in the treatment of prolapse.

### An Analysis of 43 LeFort Operations

The present report comprises a critical analysis of 43 instances of genital prolapse treated by means of almost complete colpocleisis at the Mount Sinai Hospital during the thirteen-year period, 1934 to 1946, inclusive. The indication for the operation in each patient was the presence of complete genital prolapse. Of the 43 patients, 36 (83.7 per cent) had had procidentia for from six months to thirty years; the remaining 7 (16.3 per cent) had suffered from vaginal prolapse for from four to twenty-five years following hysterectomy.

\*Presented at a regular meeting of the Philadelphia Obstetrical Society, Nov. 6, 1947.

### Marital Status and Age of the Patients

The importance of carefully explaining the anticonital nature of the operation to the patient cannot be overestimated. It should be painstakingly elucidated preoperatively, irrespective of the patient's age and marital status. One of our patients, a 58-year-old divorcee at the time of the LeFort operation, returned four years later as a newlywed and reasonably requested that the vagina be reconstructed for coital function. The primary prerequisite for the LeFort operation is that the sexual life of the patient must be completely and irrevocably renounced. If the patient is still married, it is imperative that the consent of the husband be obtained, irrespective of his age. In this series of 43 patients, 20 (46.5 per cent) were married, 20 (46.5 per cent) were widowed, and 3 (7.0 per cent) were divorced. Only one patient of the 43 was under 50 years of age; the majority were well over sixty (Fig. 1).

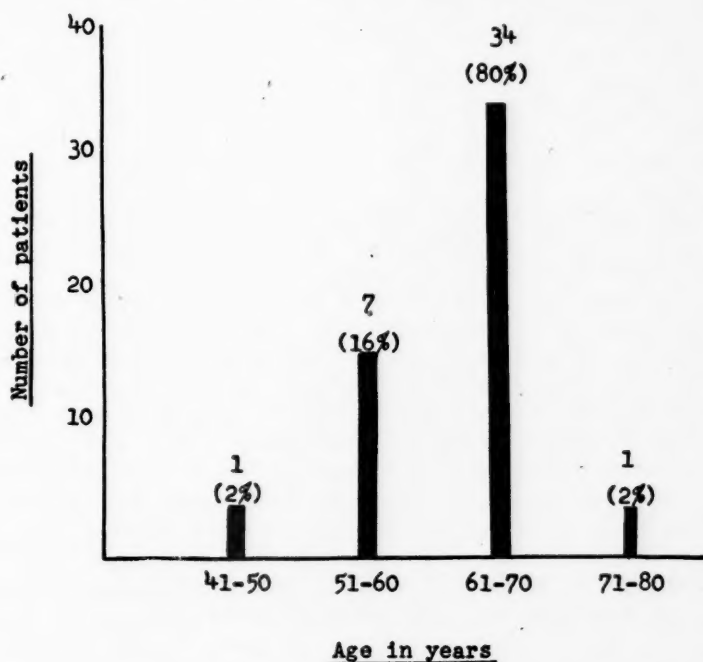


Fig. 1.—Age incidence of 43 patients subjected to the LeFort operation.

### Associated Conditions

The complicating conditions customarily found in elderly women were encountered in one-half of the group (Table I). Seventeen of the 43 patients (39.5 per cent) had hypertensive cardiovascular disease of varying degrees. Six of these 17 were definitely poor surgical risks. Five of the series (11.6 per cent) had diabetes mellitus, requiring special pre- and postoperative care.

Conditions requiring additional surgical procedures at the time of the LeFort operation were present in 16 of the 43 patients. The most frequent of these was chronic cervicitis which required amputation of the cervix in 12 of the 36 patients in whom the uterus was present. Hemorrhoidectomy was indicated on two occasions; excision of a mammary fibroadenoma was performed once; and bilateral ligation of the saphenous vein was necessary in one patient.

### Operative Technique

The 43 LeFort operations herein analyzed were performed by the authors with little variation in the technique. The anesthesia employed was selected according to the individual needs and included spinal, caudal, ether inhalation, intravenous pentothal, and local infiltration with 1 per cent solution of novocaine. A perineorraphy was included in each operation, and, in twelve instances, as noted previously, amputation of the cervix was also done. The cervical amputations were of the circular type and constituted the initial phase of the operation.

TABLE I. INCIDENCE OF COMPLICATING CONDITIONS IN 43 PATIENTS SUBJECTED TO THE LEFORT OPERATION

ASSOCIATED CONDITION	NO. OF PATIENTS	PERCENTAGE
I. Medical:		
Hypertensive cardiovascular disease	17	39.5
Diabetes mellitus	5	11.6
II. Surgical:*		
Chronic cervicitis	12	27.9
Hemorrhoids	2	4.6
Fibroadenoma of breast	1	2.3
Varicose veins	1	2.3

\*Each was surgically corrected at the time of LeFort operation.

The LeFort operation begins with the denudation of the anterior vaginal wall, the cervix being drawn downward by means of traction sutures. A rectangular, snowshoe-shaped area of vaginal mucosa is excised, extending from 2 cm. above the external os to within 1 cm. of the external urethral meatus. The posterior vaginal wall is denuded in a similar manner with the important exception that the lowermost portion of the rectangle joins the butterfly-wing type of denudation required for the perineorraphy. Thus, a strip of vaginal mucosa, approximately 2 cm. in width, remains across the portio and continues laterally, widening as it nears the introitus on each side.

Beginning with the transverse strip of mucosa of the portio and following with the lateral strips, the anterior and posterior margins of the vaginal mucosa are sutured to each other with interrupted catgut sutures (No. 1 chromic). The latter are so placed that they both enter and emerge on the mucosal surface, permitting the knots to lie within the new vaginal channel. As the edges of the portio are sewn together, the cervix disappears from view and the uterus recedes upward. During the operation, the relaxed posterior vaginal wall is repaired in the usual manner. The mucosa-lined, inverted, U-shaped channel finally extends upward from one side of the introitus to the opposite side. The transverse bar of the inverted U-shaped channel is below the cervix.

In the twelve patients in whom the cervix had been amputated and reconstructed as the first step in the operation, drainage was established by several strands of silk-worm gut extending the entire length of the inverted U-shaped channel. These were withdrawn at the end of the first postoperative week.

The care of the patients postoperatively is not exacting. The only special measure is the daily instillation of one-half ounce of a 2 per cent aqueous solution of mercurochrome into the channel by means of a small catheter and syringe. The patients are encouraged to be active and are permitted to be out of bed on the third postoperative day. A full diet is allowed as soon as the patient desires. Bowel function is encouraged with mineral oil. An enema is given on the second postoperative day. Hospitalization is generally less than two weeks.



### Results

No mortality occurred in this series of 43 patients. Ten of the group (23.2 per cent) presented postoperative complications as follows: urinary tract infection in five, fever of undetermined origin in two, infected perineorraphy wound in one, pneumonia in one, and coronary occlusion in one. Excepting the prolonged stay of these ten patients, the average number of hospital days for each patient was thirteen. At the time of discharge from the hospital, the functional and anatomic results were excellent in all patients.

Thirty-eight of the 43 patients were followed up satisfactorily for from two to eleven years. There was only a single failure—recurrence of the prolapse during the first postoperative year in a 68-year-old woman who had had a vaginal hysterectomy four years prior to the LeFort operation. She was subsequently cured by means of *total* vaginal closure. One patient, though relieved of the prolapse, developed partial incontinence of urine. This was ascribed to the surgeon's failure to form a high perineal body. The low perineal body produced undue traction on the internal vesical sphincter. Re-operation corrected the defect.

Four of the 38 followed-up patients died more than a year after the LeFort operation of unrelated causes—three of heart disease and one of carcinoma of the stomach.

Three of the 38 patients subsequently developed uterine hemorrhage, a phenomenon unrelated to the partial colpocleisis but dramatized by it because of the inaccessibility of the uterus for examination. The histories of these three patients, illustrating the management of uterine bleeding in women previously subjected to the LeFort operation, are herewith briefly outlined:

CASE 1.—Mrs. A. R., widow, aged 68 years, underwent a LeFort colpocleisis in September, 1937. She remained well for eighteen months, at which time metrorrhagia appeared. Not being able to perform either a diagnostic curettage or cervical inspection because of the partially closed vagina, we were forced to do an abdominal panhysterectomy in order to exclude the presence of carcinoma which, to our chagrin but great relief, was not present. The patient continued to be free from vaginal prolapse, but died of a coronary occlusion three years later.

CASE 2.—Mrs. S. L., widow, aged 53 years, had a LeFort colpocleisis in October, 1935, with an excellent result. Metrorrhagia appeared in March, 1944, at which time abdomino-rectal examination disclosed the uterus to be enlarged to that of a three months' gestation. Because the patient had previously received estrogen therapy for menopausal symptoms, the diagnosis of hematometra was entertained. Nevertheless, because carcinoma of the uterine fundus could in no way be excluded diagnostically, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed without disturbing the previous partial colpocleisis. The uterus contained an adenocarcinoma. Postoperative x-radiation was administered in the usual manner. When last examined, in March, 1947, the patient was free from symptoms, exempt from evidence of metastases, and without any degree of vaginal prolapse.

CASE 3.—Mrs. E. Z., widow, aged 66 years, was subjected to LeFort colpocleisis, with excellent result, in July, 1940. Metrorrhagia appeared in February, 1947, but has not recurred since then. The patient is currently being regarded with "scientific apprehensive expectancy" and will be subjected to abdominal hysterectomy should the metrorrhagia recur. Papanicolaou vaginal smears are negative.

There is an obvious contraindication to the use of estrogen in women who had been previously subjected to partial colpocleisis, as illustrated in the histories just cited. If uterine bleeding occurs, there is no possibility of distinguishing benign, estrogen-evoked metrorrhagia from that caused by carcinoma. An abdominal hysterectomy must perforce be done. On the other hand,

the incidence of carcinoma of the uterine fundus is not so high, especially in women beyond the age of 65 years, to be a deterrent to the use of the LeFort operation when definitely indicated.

### Summary

1. The principles underlying the surgical treatment of uterovaginal prolapse are briefly enumerated.
2. The indications for the LeFort colpocleisis, as one of the forms of surgical treatment, are stated, and the history of the operation reviewed.
3. The results attained in 43 patients subjected to the LeFort operation are analyzed, noting an anatomic failure in one patient and a functional failure in another.
4. The authors' technique of colpocleisis, including a circular amputation of the cervix as part of the operation when indicated, is described.
5. A singular disadvantage of the operation is the later inaccessibility of the uterus in the event of subsequent metrorrhagia, as evidenced by the histories of three patients in the group of 43 reported. The importance of avoiding estrogen administration for fear of inducing diagnostically disturbing, uterine bleeding in women who have had a LeFort operation is emphasized.

### References

1. Wallingford, A. J.: *AM. J. OBST. & GYNEC.* 38: 489, 1939.
2. Wosika, P. H., and Maher, C. C.: *AM. J. OBST. & GYNEC.* 38: 684, 1939.
3. LeFort, L.: *Ann. de gynéc.* 7: 299, 1877.
4. Quoted by Rice, A. E.: *Maryland Med. J.* 10: 769, 1884.
5. Rubovits, W., and Litt, S.: *AM. J. OBST. & GYNEC.* 29: 222, 1935.  
Phaneuf, L. E.: *AM. J. OBST. & GYNEC.* 30: 544, 1935.  
Adair, F. L., and DaSef, L.: *AM. J. OBST. & GYNEC.* 32: 218, 1936.  
Masson, J. C., and Knepper, P. A.: *AM. J. OBST. & GYNEC.* 36: 94, 1938.  
Collins, C. G., and Lock, F. R.: *Am. J. Surg.* 53: 202, 1941.

21ST AND SPRUCE STREETS.  
2116 SPRUCE STREET.

### Discussion

DR. BENJAMIN LEFF.—The advantages of partial colpocleisis are that the operation is not time consuming and may, if necessary, be done under local anesthesia. Since many of these patients are old and poor surgical risks, these are items of no little importance. In contrast to the advantages, its disadvantages are, first and foremost, that the uterus is encased back of a closed vaginal vault with only a narrow, and at best, inadequate channel for drainage. Subsequent pathology developed in the uterus is not likely to be discovered early, and is difficult to treat. The operation is palliative and does not in any way correct the distorted anatomy causing the condition. The uterus is given a shelf on which to rest within the vaginal tube. The attenuated ligaments and the retrodisplacement of the uterus, which exist in most of these cases, remain the same. It is noteworthy that of the 38 cases followed up, three developed metrorrhagia, an incidence of 8 per cent.

Because of the disadvantages stated, we have not favored this operation. On several occasions, when the patient's physical condition warranted, we have done total colpocleisis following vaginal total hysterectomy. When the patient's condition does not warrant subjecting her to the hazards of anesthesia, we are in accord with Emil Novak, who states, "I feel that when the condition of the heart, lungs, or kidney is sufficiently grave to contraindicate general anesthesia, the operation is rarely justified, and it is better to treat the patient palliatively with a pessary."

Even in the worst type of prolapse, with little or no pelvic floor left to support a pessary, we have found that the ball-and-stem pessary slung from a belt around the waistline has given adequate support.

The fact that a number of different operative procedures for the correction of this condition are practiced by various clinics is adequate proof that there has been no single operation devised that completely meets the needs in all cases. In the final analysis, each case must be evaluated as to its individual requirements. The Fothergill-Manchester operation, with or without the Gilliam shortening of the round ligaments and shortening of the uterosacral ligaments, is probably the nearest approach to a perfect anatomic restoration to normalcy. When a short operative procedure is indicated, we favor the Watkin's interposition or the Fothergill shortening of the cardinal ligaments.

DR. ROBERT TAUBER.—In the last few years I have performed five LeFort operations with excellent results. There is no doubt that the operation has its field and cannot be replaced successfully in certain cases by any other surgical procedure. I described the modified technique which I used in my cases in detail in the *Annals of Surgery*, 125: 334, 1947.

DR. CLARENCE C. BRISCOE.—A patient on whom a LeFort operation had been performed bled following stilbestrol therapy which was prescribed despite the fact that she was some twenty-five years past the menopause. A pipette was inserted into each lateral gutter and the material obtained examined with the Papanicolaou stain. Bleeding stopped when stilbestrol was discontinued and subsequent Papanicolaou stains have been negative. It is suggested that the Papanicolaou stain may be useful in preventing unnecessary surgery in similar patients who have received estrogenic therapy.

DR. A. HERBERT MARBACH.—I would like to know more about the preoperative treatment of these patients. In ten colpocleisis cases done on our service we have had difficulty with two. These were early in the series and we felt that we were doing them on patients who were not adequately prepared for this type of surgery. At the present time we prepare our patients with large doses of Vitamin B complex, large doses of vitamin C, and prime the patient for a period of at least two weeks with stilbestrol, 5 mg. daily, until the time of operation.

I wonder if this is a factor. How does Dr. Israel feel about the preoperative treatment of these patients?

DR. GEORGE HAHN.—I had an experience two years ago with a patient who had had a vaginal hysterectomy, and the prolapse recurred. The vaginal wall was again brought together by means of a LeFort type colpocleisis, and no gutters left on either side because there was no cervix to produce vaginal drainage. So far the patient is well.

DR. ISRAEL (Closing).—Many of the opinions expressed are in consonance with the views of our paper. The question concerning cervical biopsy is proper. However, we must have been lucky, for none of the twelve cervixes we amputated were malignant. The question concerning the preoperative preparation of these patients requires emphasis. Each of these patients had at least five days, more commonly a full week, of preoperative preparation which included daily cleansing of the vagina with some mild antiseptic solution and the maintenance of the prolapsed organs in good position. The suggestion of following the post-LeFort patient who shows bleeding, presumably from the hidden uterus, by vaginal smears is a good one. It could well be that this cytological technique would aid the puzzled gynecologist in his decision to perform abdominal hysterectomy.

DR. MAZER (Closing).—Dr. Leff refers to the type of genital prolapse wherein the Fothergill or the interposition operation may be employed successfully. However, when the genital prolapse is complete, as seen in some elderly women, or when the vagina is completely prolapsed following a hysterectomy, neither the Fothergill nor the interposition operation can do any good. In such cases the LeFort operation is indicated, if marital relationship is no longer a factor.

## CIRCULAR PROLAPSE OF THE URETHRA\*

JOSEPH H. ZEIGERMAN, M.D., AND ROBERT A. KIMBROUGH, JR., M.D.,  
PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology of the Graduate School of Medicine,  
University of Pennsylvania)

**P**ROLAPSE of the female urethra is a rare condition and although the volume of literature on the subject has increased considerably in recent years, most of it has come from Continental clinics. During the last half century, only twenty-two cases of prolapse of the female urethra have been reported in the United States, twelve by gynecologists and ten by urologists; almost one-half this number (9 cases) were reported in 1945.<sup>11, 16</sup>

The following is a list of the cases reported in the United States.

TABLE I

AUTHOR	CASES	AGES	YEAR REPORTED
Bagot <sup>1</sup>	1	50	1897
Hepburn <sup>4</sup>	2	Adults, age not given	1920
Livermore <sup>7</sup>	1	63	1921
Jacoby <sup>5</sup>	1	7	1925
Dannreuther <sup>2</sup>	1	54	1926
Hepburn <sup>4</sup>	1	5	1927
Loux <sup>8</sup>	1	10	1927
Livermore <sup>7</sup>	1	8	1931
Ormond <sup>12</sup>	1	53	1934
Keefe <sup>6</sup>	1	53	1935
Epsteen and Strauss <sup>3</sup>	1	60	1937
Mayer <sup>9</sup>	1	54	1938
Miller <sup>11</sup>	4	49, 53, 57, 72	1945
Zeigerman <sup>16</sup>	5	2, 43, 44, 57, 62	1945
Total	22		

The literature in 1945 contained 311 collected cases<sup>16</sup> as follows:

TABLE II

AUTHOR	YEAR	NO. OF CASES
Solingen <sup>14</sup>	1732	1
Sauferlin <sup>15</sup>	1732-1926	270
Epsteen and Strauss <sup>3</sup>	1926-1937	300
Zeigerman <sup>16</sup>	1937-1945	311

Since 1945, eight additional cases were reported<sup>10, 11, 13</sup> which, with the two herein described, make a total of 321 cases.

The lesion occurs at any age and is attended by tumor, pain, bleeding, and urinary complaints. The incidence is about 47 per cent in the age group of 5 days to 18 years; about 18 per cent between 18 to 45 years, and in women over

\*Read at a meeting of the Philadelphia Obstetrical Society, Dec. 5, 1947.



45 years, about 35 per cent. The greatest incidence is between 8 and 12 years of age and 60 to 65 years. The youngest patient whose case was reported was a child 5 days old, and the oldest a woman of 92 years.

The symptoms and size vary with the extent of the circulatory disturbance. There may be necrosis and even gangrene of the prolapsed mass. The urethral orifice may be difficult to find as it often deviates to one side of the tumor mass, even necessitating in some cases a general anesthetic to disclose it. A biopsied specimen usually shows acute or chronic inflammation, engorgement, thrombosis, and, occasionally, hypertrophied submucous glands. The muscle layer is usually absent.

The histories of the two patients seen by us recently are briefly recorded here.

CASE 1.—No. 175561, Graduate Hospital, University of Pennsylvania. Admitted, Dec. 17, 1946, discharged, Jan. 20, 1947.

J. J., 9-year-old Negro girl, admitted with vaginal bleeding, painful urination, and a painful lump in the vagina. The child was in perfectly good health until one week ago, when she was kicked in the vulva by her 2-year-old sister. Following the injury, there was a small amount of bleeding and pain in the vagina; this had continued every day since the injury.



Fig. 1.—Circular prolapse of the urethral mucosa protruding from the vaginal introitus in a 9-year-old girl.

Vaginal inspection revealed a red fleshy mass protruding from the vagina and filling the introitus. This mass was first thought to be a hematoma of the right rim of the external urinary meatus due to trauma. Under general anesthesia, the prolapsed urethra was exposed and a catheter introduced into the meatus, confirming the diagnosis of circular prolapse of the urethral mucosa. She was confined to bed and after application of compresses and bed rest for three weeks, the lesion was excised by circumcision. Chronic 0 sutures were placed about the urethral orifice, one anteriorly, one posteriorly, and one on either side as a guide in subsequent resection. The excess mucosa was then excised in quadrants to the level of the catgut and approximated with two additional interrupted sutures of fine catgut placed between the original quadrant sutures. A Foley catheter remained in the bladder for three days. The convalescence was uneventful. Studies of the bladder and renal function revealed no abnormality. A re-examination eight months later showed no recurrence of the prolapse and the patient had no complaints.

CASE 2.—No. 75187, Pennsylvania Hospital. Admitted April 20, 1946, discharged, April 27, 1946.

D. W., a 9-year-old white girl was admitted with pain, vaginal bleeding, and discomfort on urination. She had had recurrent attacks of spotting of blood from infancy until she was five years old. Six weeks prior to admission, she fell from a bicycle and had bleeding from the vagina for two weeks. Vaginal inspection revealed a tumor mass which was thought to be a traumatic injury of the anterior vaginal wall protruding through the hymenal ring. On subsequent examinations, the lesion proved to be a circular prolapse of the urethral mucosa. After application of compresses and bed rest for two weeks, the lesion was excised by circumcision. Silver wire sutures No. 36 were placed about the urethral orifice; one anteriorly, one posteriorly, and one on either side as a guide in subsequent resection. The excess mucosa was excised in quadrants to the level of the silver wire and the cut edges were approximated with fine catgut. The silver wires were then removed. A Foley catheter remained in the bladder for four days. The convalescence was uneventful and the patient was discharged in good condition. A re-examination nine months later showed no recurrence of the prolapse.

Altogether seven cases of urethral prolapse had been treated by us over a period of eight years with good results. The following is a résumé of age, symptomatology, duration of symptoms, precipitating causes, and the results of the operation, in each of our cases.

TABLE III. ANALYSIS OF THE INDIVIDUAL CASES

AGE	ACUTE SYMPTOMS	DURATION OF ACUTE SYMPTOMS	DURATION OF CHRONIC SYMPTOMS	PRECIPITATING CAUSE	
				DIRECT	INDIRECT
2	Vaginal bleeding Painful lump in vagina Painful urination	1 week	-----	-----	Persistent cough.
9	Vaginal bleeding Painful lump in vagina Painful urination	1 week	-----	Kicked in vulva	-----
62	Vaginal bleeding Painful lump in vagina Painful urination	1 week	-----	-----	Chronic constipation
9	Vaginal bleeding Painful lump in vagina Painful urination	2 weeks	Recurrent vaginal staining for 5 years.	Fell off bicycle.	-----
57	Vaginal bleeding Painful lump in vagina Painful urination	1 day	Lump in vagina without symptoms several years.	Unknown	Unknown
43	Vaginal bleeding Painful lump in vagina Painful urination	4 days	Lump in vagina without symptoms for 4 years.	-----	Diarrhea
44	Vaginal bleeding Painful lump in vagina Painful urination	1 week	Intermittent symptoms 3 years.	-----	Cystitis

The onset, as observed in the majority of cases herein reported, points to a pre-existing lesion of the urethra with minimal symptoms for several years, followed by direct or indirect trauma, which produced the acute symptoms.

Direct trauma was the precipitating cause in the two nine-year-old girls, an abnormal increase in intraabdominal pressure due to persistent cough, chronic constipation, and diarrhea in three other patients, and a subacute cystitis of long standing in the sixth case.

### Treatment

The seven cases seen by us were treated by excision of the prolapsed mucosa and suturing the cut edges.

The technique of resection used in the last two cases has greatly simplified this operation. The suture ligatures which were placed at 3, 6, and 9 o'clock on the face of the prolapse at the mucocutaneous junction served as a guide in the subsequent resection, preventing the retraction of the mucosa and diminishing the loss of blood.

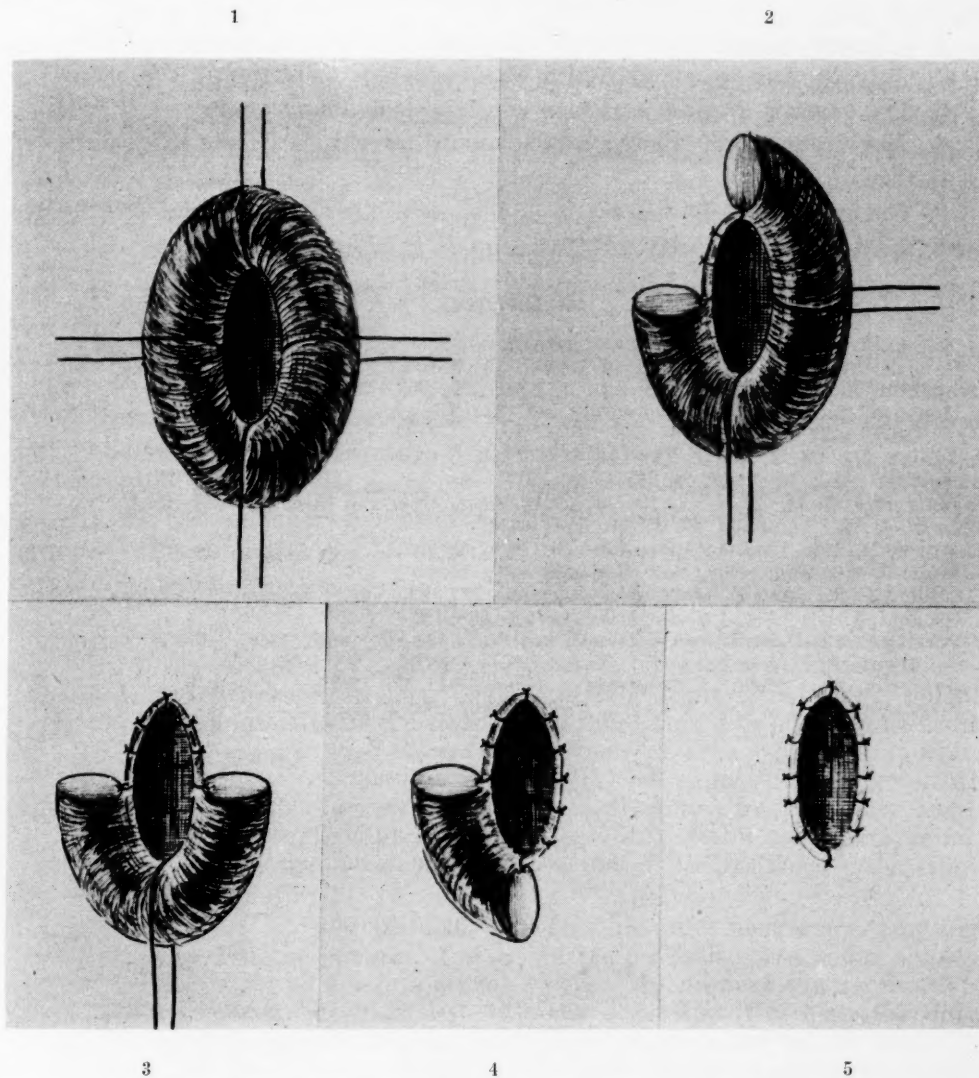


Fig. 2.—Resection of the circular prolapse in quadrants. Guide sutures tied. Single sutures added. 1. Showing guide sutures. 2. First quadrant removed. Guide sutures tied. Single sutures added. 3. Second quadrant removed. Single sutures added. 4. Third quadrant removed. Single sutures added. 5. Fourth quadrant removed. Single sutures added.

In our experience with this condition, it was found that simple excision of the prolapsed mucosa has given excellent results; in none of these cases was there any recurrence.

TABLE III. FOLLOW-UP REPORT

AGE	DIAGNOSIS	OPERATION	YEAR	RESULTS
43	Circular prolapse	Circumcision	1939	No recurrence
62	Circular prolapse	Circumcision	1940	No recurrence
57	Circular prolapse	Circumcision	1942	No recurrence
2	Circular prolapse	Circumcision	1944	No recurrence
9	Circular prolapse	Circumcision	1946	No recurrence
9	Circular prolapse	Circumcision	1946	No recurrence

### Summary and Conclusions

1. 321 cases of urethral prolapse have been reported in the world literature.
2. Only 22 cases were reported in this country during the past 50 years.
3. The onset is gradual and may continue over many years.
4. The circumcision operation is adequate for the treatment of prolapse of the urethra.
5. The excision of the mucosa in quadrants diminishes bleeding, gives better approximation of tissue, and serves as a guide in resection.

### References

1. Bagot, W. S.: Med. News, June 5, 1897.
2. Dannreuther, W.: AM. J. OBST. & GYNEC. 11: 468, 1926.
3. Epstein, A., and Strauss, B.: Am. J. Surg. 35: 563, 1937.
4. Hepburn, T. N.: Surg., Gynec. & Obst. 31: 83, 1920, also Surg., Gynec. & Obst. 44: 400, 1927.
5. Jacoby, N.: M. J. & Rec. 122: 131-132, 1925.
6. Keefe, J. W.: J. A. M. A. 69: 1935, 1917.
7. Livermore, G. H.: J. Urol. 25: 99, 1931; Surg., Gynec. & Obst. 32: 557, 1921.
8. Loux, H. R.: Atlantic M. J. 31: 181, 1927.
9. Mayer, M. M.: Urol. & Cutan. Rev. 42: 783-792, 1938.
10. Moir, J. C.: Proc. Roy. Soc. Med. 37: 436, 1944.
11. Miller, J. R.: AM. J. OBST. & GYNEC. 49: 591-595, 1945.
12. Ormond, J. K.: AM. J. OBST. & GYNEC. 28: 458, 1934.
13. Pereira Silva, J. H.: Obst. & Gynec. Latino 3: 848-864, Nov., 1945.
14. Solingen: Ref. from Sauferlin, H., No. 15.
15. Sauferlin, H.: Ztschr. f. Geburtsh. u. Gynäk. 94: 630, 1929.
16. Zeigerman, J. H.: Urol. & Cutan. Rev. 44: 403-409, 1945.



## A CHEMICAL TEST FOR PREGNANCY

WILBUR A. RICKETTS, M.D., F.A.C.S., RICHARD M. CARSON, B.S., AND  
REUBEN R. SAEKS, B.S., DAYTON, OHIO

THE early diagnosis of pregnancy, always a matter of wide interest in obstetric practice, has become more important than ever, since we have learned so much about its physiologic implications. As a consequence of early diagnosis, it becomes possible better to advise the patient with respect to hygienic, psychic, dietary, and other adjustments to pregnancy. It permits us to apply safeguards to protect mother and child against possible adverse effects resulting from endocrine or other disturbances, or from an unpropitious Rh relationship.

A simple, rapid, and reliable office test has been developed by two of the authors (Carson and Saeaks), and used in collaboration with the senior author in over 400 cases.

The test is based on the established finding that during normal pregnancy, histidine is excreted in substantial amounts. This knowledge has been used before in diagnostic procedures, but earlier tests have had the disadvantages of either overwhelming unwieldiness or insufficient accuracy.

Essentially, the test consists of the following steps: (1) control of specimen, (2) dilution, (3) removal of substances which interfere with the test, and (4) detection of histidine by Knoop's Method. One or more tests can be run in a period of twenty to thirty minutes.

1. *Control of Specimen.*—It has been observed by the authors and others that after a heavy intake of protein, the urine of a nonpregnant woman may show histidine, but in relatively small amounts. They have found that if reliable results are to be obtained with a histidine test, there should be at least one urination after the ingestion of food before the specimen is taken. An early morning specimen is preferable. It has also been observed that histidine is frequently present in the urine during menstruation as well as two to three days before the onset of the flow. Therefore, it would seem inadvisable to use a specimen taken near the end of the menstrual cycle because of the likelihood of obtaining false positive results.

2. *Dilution.*—It is often possible to detect histidine in specimens of high specific gravity. For the purpose of avoiding the possibility of the test showing histidine in the urine of a nonpregnant woman, we prepare the specimen by diluting it to a concentration so low that the small amount of histidine which might occur in urine in such an instance will not be indicated by the test. The amount by which the urine is to be diluted is determined by both its specific gravity and pH. By experiment, we have found that an alkaline specimen should be diluted with water to a specific gravity of 1.009, and an acid specimen should be diluted to a specific gravity of 1.005.

3. *Removal of Interfering Substances.*—A 5 c.c. portion of the diluted specimen is used for making the test. Phosphates are precipitated with a 10 per cent barium chloride solution. Nitrites are oxidized with 0.1 N potassium permanganate reagent. Solids are removed by filtration.

4. *Detection of Histidine.*—The clear test solution is brominated as in Knoop's method.<sup>1</sup> A reagent of bromine in 33 per cent acetic acid is employed, and an excess of bromine is maintained in the mixture for about ten minutes. One-half cubic centimeter of an ammonium carbonate reagent (3 per cent ammonium carbonate in 2:1 ammonium hydroxide) is then added and the mixture heated at about 95° C. for several minutes. If sufficient histidine is present, a red-purple or bright pink color develops which fades upon standing.

### Results of the Chemical Pregnancy Test

More than 400 determinations were made by the Carson-Saeks chemical procedure for histidinuria. All specimens were obtained from the practice of the senior author, and results were verified clinically by him. Tests were performed by Carson and Saeks.\* Not all specimens were controlled as to diet, time of collection, etc. The results, shown in Table I, indicate an accuracy of 95.1 per cent in clinically positive cases and 92.6 in clinically negative cases. In Table II is presented a tabulation of results as correlated to the time of last menstruation prior to collection of the specimen. Eight male urines were tested to afford an additional check on the specificity of the reaction.

TABLE I. SUMMARY OF CLINICAL DATA OBTAINED FROM TESTS BY CARSON-SAEKS METHOD

CLINICAL FINDING	NO. OF CASES	NUMBER		PER CENT	
		CORRECT	INCORRECT	CORRECT	INCORRECT
Positive	268	255	13	95.1	4.9
Negative	163	151	12	92.6	7.4
Total	431	406	25	94.2	5.8

TABLE II. SUMMARY OF DATA CORRELATED WITH DATE OF CESSATION OF MENSTRUATION

PERIOD SPECIMEN TAKEN	POSITIVE				NEGATIVE				TOTALS			
	NUMBER		PER CENT		NUMBER		PER CENT		NUMBER		PER CENT	
	COR-RECT	INCOR-RECT	COR-RECT	INCOR-RECT	COR-RECT	INCOR-RECT	COR-RECT	INCOR-RECT	COR-RECT	INCOR-RECT	COR-RECT	INCOR-RECT
First month	24	2	92.5	7.5	30	1	96.7	3.3	54	3	94.7	5.3
Second month	68	1	98.7	1.3	7	3	70.0	30.0	75	4	94.9	5.1
Third month	56	-	100	-	-	4	-	100	56	4	93.3	6.7
Fourth month	35	1	97.4	2.8	-	-	-	-	35	1	97.2	2.8
Fifth month	13	-	100	-	1	-	100	-	14	-	100	-
Sixth month	2	-	100	-	1	1	50	50	3	1	75	25
Seventh month	3	-	100	-	-	-	-	-	3	-	100	-
Eighth month	1	-	100	-	-	1	-	100	1	1	50	50
Last menstruation unknown	30	6	83.3	3.7	91	1	98.9	1.1	121	7	94.5	5.5
Postpartum	-	1	-	100	20	-	100	-	20	1	95.2	4.8
Male urine	-	-	-	-	8	-	100	-	8	-	100	-
Totals	• 232	11	94.7	5.3	158	11	93.6	6.4	390	22	94.4	5.6

For the sake of comparison, the accuracy of this test is compared with that of other methods of diagnosis. The chemical test of Voge,<sup>2</sup> modified by Kapeller-Adler,<sup>3, 4</sup> is based on the finding of histidinuria, as is our test. The test of Visscher-Bowman<sup>5</sup> is based on the reducing properties of gonadotropin. The Guterman test<sup>6</sup> depends on a color reaction of urinary pregnandiol. The criticism has been voiced<sup>7</sup> that (1) the concentration of pregnandiol in early pregnancy is too low to make it of value as an early diagnostic test, and (2) the incidence of false positive reactions is high in cases of delayed menstruation. The standard

\*We are indebted to Westerfield Pharmacal Co., Inc., for their assistance and supplies of materials.

biological tests (Aschheim-Zondek and Friedman) are, of course, highly accurate; however they are not suitable for use as office procedures.

Table III presents a comparison of some of the tests used in the early diagnosis of pregnancy with the Carson-Saeks method.

TABLE III. COMPARISON OF TESTS FOR EARLY DIAGNOSIS OF PREGNANCY

	CASES	CLINICAL POSITIVES	CLINICAL NEGATIVES
		RANGE OF ACCURACY	RANGE OF ACCURACY
<i>Chemical tests</i>			
Histidinuria			
Carson-Saeks Test	412	94.7%	94.4%
Voge and Kapeller-Adler (reviewed by Mello <sup>8</sup> )	2,350	63%-95.2%	75%-98%
Visscher-Bowman Test (revised by Mello <sup>8</sup> )	961	66%-100%	
<i>Biological tests</i>			
Aschheim-Zondek (cited by Weisman <sup>9</sup> )	2,807	94%	97%
Friedman Test	About the same as Aschheim-Zondek test		

### Discussion

The histidine excretion test for the early diagnosis of pregnancy is based on established findings that histidine metabolism is significantly altered during pregnancy. Normally, histidine is converted by the liver into histamine.<sup>10</sup> However, during pregnancy, it is excreted in the urine, possibly because of the effect of prolactin on the ability of the liver to inactivate histidine,<sup>3</sup> or a lowering of the renal threshold for histidine in the pregnant woman.<sup>11</sup>

The histidine test for pregnancy has been in use for about fifteen years; previous results have been variable for two principal reasons. (a) The diet of the patient in regard to protein intake was not controlled prior to collection of the specimen; and (b) tests were performed on concentrated urines which reduced sensitivity and specificity of the test.

Certain pathologic conditions may lead to false results. When pregnancy is complicated by eclampsia, histidine disappears from the urine.<sup>12</sup> Endocrine disturbances (thyroid, pituitary, or adrenal) may interfere with the specificity of the test.<sup>11, 13</sup> Urinary excretion of amino acid may occur in persons with extensively impaired hepatic function or those exhibiting severe tissue autolysis.<sup>14</sup> The existence of nutritional deficiencies may cause a weak positive or false negative reaction in pregnant individuals.

While these factors appear to be detrimental to the accuracy of the test, it may be considered that false reactions may serve as a guide to further study of the patient with a view to possible diagnosis of endocrine or other disturbance. Studies are now in progress to extend our knowledge of the significance of false findings.

It must be noted that not all the urine specimens were obtained under optimal conditions. One might expect a greater degree of accuracy if care were taken to assure in every case that (1) the specimen was obtained early in the morning or several hours after ingestion of a protein-rich meal; and (2) the patient had voided urine after such a meal before the specimen is collected.

### Summary

A new chemical test for pregnancy is proposed. The test depends upon a modified procedure for the estimation of histidine excretion in pregnancy. The physiologic basis of the test is discussed. Studies on more than 400 cases indicate that the method is rapid, simple, and accurate enough to justify its use, particularly as an office procedure.

### References

1. Knoop, F.: Beitr. z. chem. Phys. u. Path., **7**: 356, 1907-08.
2. Voge, G. I. B.: Brit. M. J. **1**: 829, 1929.
3. Kapeller-Adler, R., and Haas, F.: Biochem. Ztschr. **280**: 232, 1935.
4. Kapeller-Adler, R., and Herrmann, H.: Klin. Wchnschr. **15**: 977, 1936.
5. Visscher, J. P., and Bowman, D. E.: Proc. Soc. Exper. Biol. & Med. **31**: 460, 1934.
6. Guterman, H. S.: J. Clin. Endocrinol. **4**: 262, 1944.
7. Rakoff, A. E.: M. Clin. North America **29**: 1546, 1945.
8. Mello, M. I.: Mem. Inst. Oswaldo Cruz **42**: 223, 1948.
9. Weisman, A. I.: AM. J. OBST. & GYNEC. **35**: 354, 1938.
10. Schmidt, C. L. A.: Chemistry of the Amino Acids and Proteins, Springfield, Ill., 1944, Charles C Thomas.
11. Page, E. W.: AM. J. OBST. & GYNEC. **51**: 553, 1946.
12. Page, E. W.: West. J. Surg. **51**: 482, 1943.
13. Garrod, A. E.: Inborn Errors of Metabolism, London, 1923. Bailliere, Tindall & Cox.
14. Cantarow, A., and Trumper, M.: Clinical Biochemistry, Philadelphia, 1940, W. B. Saunders Company.

1030 FIDELITY MEDICAL BUILDING



## INTERVILLOUS THROMBI IN THE PLACENTA AND THEIR POSSIBLE RELATION TO ERYTHROBLASTOSIS FETALIS

EDITH L. POTTER, M.D., PH.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, The University of Chicago, and  
The Chicago Lying-in Hospital)*

WITHIN the central part of a cotyledon in an occasional placenta is found a red laminated area measuring from a few millimeters to slightly over 2 cm. in diameter. These structures are somewhat irregular in shape but they usually assume a fairly round or cuboidal form. The neighboring villi are pushed back and none are present within the lesion. (Fig. 1.) Occasionally surrounding the central area is a peripheral zone of degenerated villi measuring 3 to 10 mm. in diameter caused by compression with a secondary degeneration due to local absence of maternal blood.

These areas have been often classed as infarcts but are better considered as thromboses since their structure is similar to that of a thrombus. The color depends on the length of time they have been present but the majority are dark red and are streaked with light yellow lamina due to local deposits of fibrin and platelets. They seem to occur ordinarily only late in pregnancy for similar structures in which blood cells have been destroyed and which are consequently yellow are uncommon.

Such thrombotic areas have generally been considered of maternal origin but the statement has been made on several occasions that they are of fetal origin and Javert<sup>1</sup> believed their presence proved that fetal blood might leak out of the vessels in the villi into the maternal circulation. He gave as proof the fact that nucleated red blood cells were thought to have been found in such areas in the placentas of infants with erythroblastosis. This statement has been widely quoted as evidence that escape of fetal blood into the maternal circulation does occur and that it may be the means of producing maternal immunization when the mother is Rh negative and the fetus is Rh positive.

The same author has further stated that retroplacental hematomas are evidence of hemorrhagic disease of the fetus and that the administration of vitamin K before the expected onset of labor should be of benefit in preventing premature detachment of the placenta.

The present study was undertaken in an attempt to determine whether these areas of intervillous thrombosis are actually composed of fetal blood or whether the cells are of maternal origin. Leucocytes are frequently found in large masses in any thrombus, due to the layering which results from the manner of deposition, and it is possible that the nuclei of lymphocytes might have been mistaken for those of immature red blood cells.

Since the areas of intervillous thrombosis are usually composed of well-preserved cells, it seemed possible to settle the problem of their origin by typing the blood of the mother, infant, and thrombus.

During 1944, 1660 placentas delivered from patients at the Chicago Lying-in Hospital were examined. These were not all delivered consecutively but during the periods of study the placentas of all patients were investigated.

The lesions described above are almost never visible on the external surface of the placenta and are found only in the central portions of the cotyledons. Consequently all placentas were placed on a board and the substance was cut with a long knife into slices approximately 1 cm. thick.

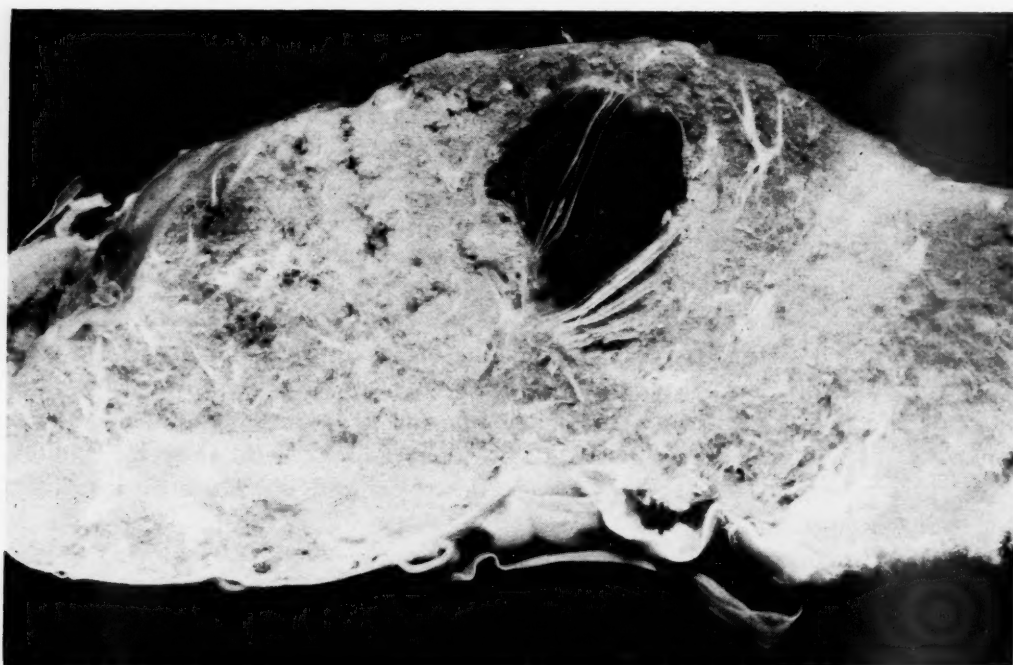


Fig. 1. Portion of placenta containing an area of intervillous thrombosis.

Among the 1660 placentas that were examined, thrombi were found in 60, an incidence of 3.6 per cent. Of these, only 4 were too old to permit typing the cells. The results of typing the blood of the mother, the blood of the umbilical cord, and the cells of the thrombus in the remaining 56 are shown in Table I.

TABLE I. RELATION OF THE BLOOD GROUP OF CELLS IN PLACENTAL THROMBI TO THE BLOOD GROUPS OF MOTHER AND INFANT

NUMBER	THROMBUS	INFANT	MOTHER
22	0	0	0
20	A	A	A
2	B	B	B
5	A	0	A
2	B	A	B
2	0	B	0
2	A	B	A
1	0	A	0

In 44 of the 56 thrombotic areas in which the cells were satisfactorily typed, the mother, thrombus, and infant were of the same blood group. Among the 12 in which the mother and infant were of different blood groups, all of the thrombi without exception were of the same group as the mother and none were of the same group as the infant.

If, in this large a group of placentas, there were no infarets composed of fetal blood, it seems reasonable to conclude that such infarets either do not exist or do so with the greatest rarity. It is the author's belief that such infarets are always of maternal origin and are unrelated to the possible etiology of erythroblastosis fetalis or hemorrhagic disease of the newborn. Consequently, the citation of the presence of such thrombotic areas as proof that fetal cells may escape from the vessels in the villi, and so escaping may be the source of maternal immunization to the Rh factor does not seem justified. The fact that these areas are not composed of fetal cells does not prove that fetal cells may not enter the maternal circulation from the villi, but if proof for such intermixture of cells is desired it must be obtained by others means.

### Summary

Examination of 1660 placentas revealed the presence of intervillous thrombosis in 3.6 per cent. Among 56 placentas in which the cells of the thrombi could be typed the blood groups of the infant, mother, and thrombus were the same in 44. In the remaining 12, in which the mother and the infant belonged to different blood groups, the cells of the thrombus were in all instances of the same type as those of the mother. The presence of such thrombi cannot be used as proof for the contention that fetal blood may escape from the villi during pregnancy and may consequently be the cause of maternal immunization when the fetus is Rh positive and the mother is Rh negative.

### References

1. Javert, C. T.: *AM. J. OBST. & GYNEC.* 43: 921, 1942.
2. Javert, C. T.: *AM. J. OBST. & GYNEC.* 40: 453, 1940.

## EXTRAUTERINE PREGNANCY AT TERM WITH DELIVERY OF A NORMAL LIVING CHILD AND LIVING MOTHER\*

FRANK S. DEMING, B.S., M.D., M.S., PHILADELPHIA, PA.

*(From the Department of Obstetrics and Gynecology, Temple University School of Medicine)*

ABDOMINAL pregnancy is a condition which is seldom, if ever, met with in a lifetime practice of obstetrics. When encountered, however, it presents a most difficult problem to the obstetrician as to management and is accompanied by an extremely high mortality to mother and child. In a review of the literature on this subject, Cornell and Lash in 1933 reported two hundred thirty-six cases of abdominal pregnancy, with a maternal mortality of 14.3 per cent. In eighty-six cases where the baby was born after the sixth month of pregnancy, there was an infant mortality of 22 per cent, while in sixty cases where the baby was born alive in the eighth or ninth month of pregnancy, the mortality was 35 per cent. In 1935, Hellman and Simon reported three hundred sixteen cases of abdominal pregnancy, in which the mother survived in two hundred twelve cases and the fetus in one hundred fifty-eight cases. In eighty cases, both mother and child survived—that is, lived eight days or longer. Woods reported a case of abdominal pregnancy with a normal living baby but the mother died within a few days after delivery from an overwhelming toxemia as a result of peritonitis. In November, 1944, Gardner reported a case in which both mother and baby survived, and the latter, weighing four pounds and fifteen ounces, was without congenital defects or anomalies. This infant died at four and one-half months, however, from pneumonia, and the mother expired two years later from a metastasizing carcinoma of the breast. Beacham, in a review of abdominal pregnancy, cites numerous instances throughout the literature where both mother and child survived. However, in a great majority of instances where the fetus was alive at birth, a neonatal death ensued in a matter of hours or days after delivery, and many of the infants showed single or multiple congenital defects.

It is, therefore, still a rarity to deliver a normal living baby free of congenital defects and to be fortunate enough to secure a satisfactory maternal result as well. Such a case was encountered at Temple University Hospital, Philadelphia, over a year ago.

### Case Report

The patient was a twenty-one-year-old Negro primigravida who presented herself at the out-patient department of Temple University Hospital approximately five months pregnant. Her history was as follows:

The patient's last menstrual period was Sept. 17, 1944. On Oct. 15, 1944, there was an episode of vaginal bleeding which lasted for two days. The flow was intermittent in character and very scanty. There were no further complaints until Dec. 23, 1944, when, after a fall in her home, apparently without abdominal trauma, the patient experienced considerable abdominal pain and complained of weakness. Since pain was more or less constant and aggravated by motion, the patient remained in bed for one week. At the end of this period, she felt no better and consulted her family physician who hospitalized her at another institution for a seventeen-day period at complete bed-rest. During this time, she continually improved, although there was still slight lower abdominal distress at times. Because of the continuation of these symptoms, she registered at the out-patient department of Temple University Hospital in the latter part of February, 1945.

On her first visit, examination revealed abdominal enlargement compatible with five months' gestation. Although there was considerable abdominal tenderness and pelvic examina-

\*Presented at a regular meeting of the Philadelphia Obstetrical Society.



tion difficult, it was noted that the cervix was soft and the uterus seemed enlarged to the size of a five months' pregnancy. Pelvimetry was adequate and the remainder of her physical examination was negative.

She was examined thereafter at three-week intervals. Pregnancy progressed and fetal heart sounds became audible on second clinic visit; patient noted fetal movement at this time. On her third visit, a mass was noted in midline just above the symphysis, which was thought to be a small fibromyoma. The abdominal distress continued but did not increase in severity.

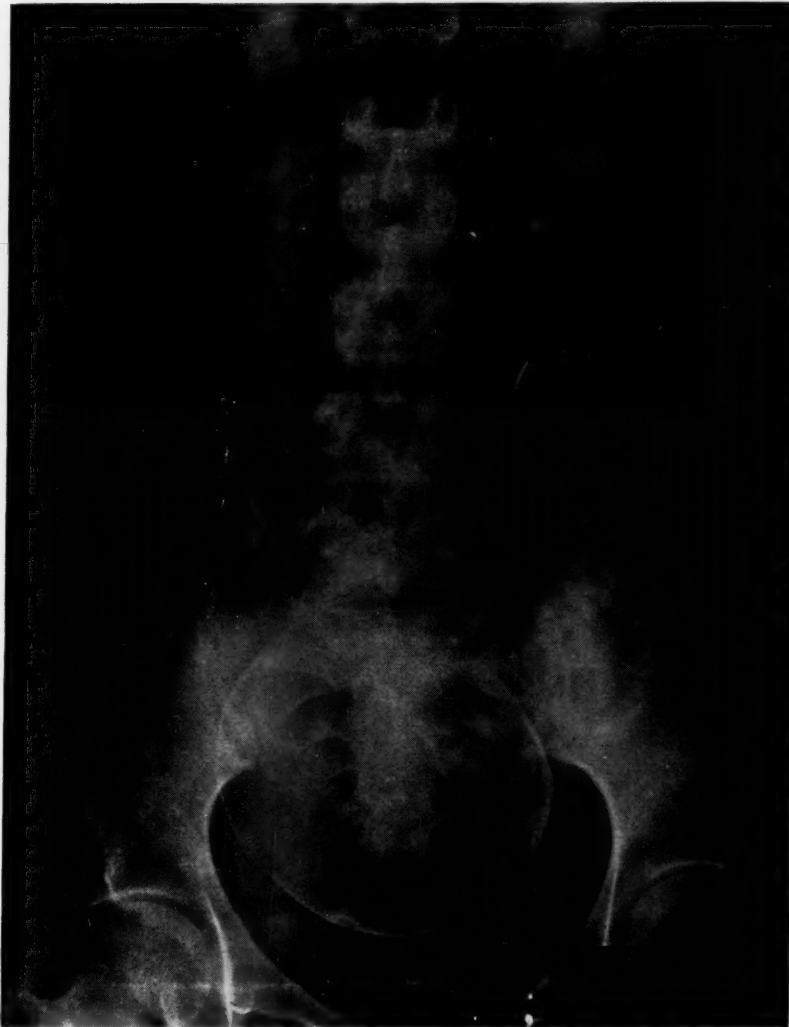


Fig. 1.—Roentgenogram taken two weeks before term.

Pregnancy continued until July 6, 1945, when the patient was hospitalized because of spotting and accentuation of her lower abdominal distress which she thought was labor. Examination showed abdominal enlargement compatible with a full-term pregnancy. There was a mass noted in midline just above the symphysis which was approximately six to eight centimeters in diameter. It was extremely tender on palpation. Fetal heart sounds were readily audible in the left lower quadrant. The position was diagnosed as left occiput anterior. Rectal examination revealed vertex at minus one station in the pelvis.

Roentgenologic report at this time read as follows:

"An intrauterine pregnancy with fetus at term lying in left occiput anterior position, vertex almost engaged. The pelvis seems ample for vaginal delivery. The placenta is situated high up in the upper segment of the uterus slightly to the left and posteriorly." (Fig. 1.)

After seventy-two hours of hospitalization, all the patient's symptoms disappeared and she was discharged. On July 26, 1945, patient was again admitted for twenty-four hours but was discharged as in "false labor." There was no bleeding on this admission.

On Sept. 2, 1945, patient was seized with severe colicky-type abdominal pain. There was again a slight bloody discharge. The pains increased in severity and frequency until twelve o'clock midnight, when patient stated they took her breath away. She was admitted to the hospital and examination revealed the patient in acute distress. Temperature 98°; pulse 95; respiration 22; blood pressure 118/72. In spite of these findings, she gave one the impression of shock. The abdomen was tense, extremely tender, slightly distended and peristalsis was absent. The mass noted formerly was acutely tender. The fetus seemed at term with back to the left in left occiput anterior position, head was thought to be engaged at plus one station and there was no cervical dilatation. Fetal heart tones were not audible. Admission blood count was: Red blood count, 4.65; hemoglobin, 12 Gm.; white blood count, 11,900. The urinalysis report was entirely negative. A diagnosis was made of placenta abruptio (partial) with the possibility of ruptured appendix and degenerating fibroid. It was decided that abdominal exploration was indicated.

*Operative Findings.*—On opening of the peritoneal cavity, a greenish-yellow exudate was encountered (subsequent culture report showed no growth), and there were about 300 to 500 c.c. of free peritoneal fluid. The appendix was normal. The uterus was noted in the midline just above the symphysis enlarged to twice normal size. The right tube and ovary were normal. The left ovary could not be visualized and the left tube was lost in the wall of a large mass which lay just to the left, and beneath the uterine body and extended from deep in the pelvis to a point just under the diaphragm. This mass seemed entirely retroperitoneal. The small bowel, sigmoid, and cecum were covered with a greenish-yellow exudate and were slightly injected, although in no way adherent to the mass. The omentum was adherent to the upper portion of the mass and large vessels were springing from this point which anastomosed over the surface of the mass with other large vessels which seemed to be springing from the mesentery of the small intestine.

An incision was made in the lower portion of the mass in the region of the left broad ligament since this area was relatively avascular. Considerable greenish-yellow exudate was encountered which was the same as that noted in the peritoneal cavity, indicating that there must have been a perforation of the sac before delivery. An eight-pound, two-ounce female fetus was extracted by breech. The infant was living, breathed readily and appeared to be entirely normal. Exploration of the sac revealed the placenta in the upper portion slightly to the left and posteriorly situated. A chromic No. 2 catgut double ligature was placed around the cord close to the placental attachment and a large Babcock sump was placed in the bed of the sac, after which the sac was closed with no attempt made to remove the placenta. Another sump drain was inserted in the right iliac fossa.

*Postoperative Course.*—The patient did well the first three days postoperatively. On the third day, the temperature was normal and the abdomen flat with active peristalsis. Drainage was slight and the sump drain to the right iliac fossa was removed. In this early postoperative period, the patient received parenteral fluids freely with 500 c.c. whole blood and sodium sulfadiazine, 2 Gm. every six hours intravenously for the first forty-eight hours. On the third day, penicillin was started, giving twenty thousand units every three hours and this was continued until a total of four million three hundred ten thousand units had been administered. From the third postoperative day, the patient ran a temperature of 101° F. to 102° F. for the next eight weeks. On the tenth postoperative day, the sump drain within the amniotic sac was removed and a large rubber catheter inserted. On the twelfth day, it was felt that an abscess was forming in the right lower quadrant area but on opening the abdomen in this site, nothing but indurated tissue was found, and no drainage was obtained. The patient drained

continually, at some times a frankly bloody drainage and on other occasions, a brownish purulent material, cultures of which showed throat-type anaerobic nonhemolytic streptococci. There was never any evidence of pointing or abscess formation in the pelvis thereafter which would be suitable for colpotomy or abdominal drainage. There was a marked anorexia for five or six weeks and considerable weight loss. A rather severe anemia developed which responded well to small frequent blood transfusions. The total period of drainage was two months. The total period of hospitalization was one hundred one days.

*Follow-Up Visits.*—The abdominal incisions were well healed and pelvic examination was normal except for considerable induration just to the left of the uterus, with adhesive bands from this point to the abdominal scar. The baby gained well, weighing fifteen pounds at five months.

At the end of a year, the child was walking and the mother seemed no worse for her experience. There still remained some induration in the left adnexal area, but no tenderness and no particular complaints.

It is interesting to note that the patient carried this pregnancy almost a year according to her menstrual history. That death of the fetus did not occur seems remarkable. Also interesting is the attachment site of the placenta, which, in this case, was high in the sac, while in most cases of this kind, attachment is usually lower and against the uterus.

### References

- Beacham, W. D., and Beacham, D. W.: *Obst. & Gynec. Survey* 1: 777, 1946.  
Cornell, E. L., and Lash, A. F.: *Internat. Abstr. Surg. Supplement, Surg., Gynec. & Obst.* 57: 98, 1933.  
Gardner, et al.: *Am. J. Surg.* 66: 161, 1944.  
Hellman, A. M., and Simon, H. J.: *Am. J. Surg.* 29: 403, 1935.  
Woods, E. B.: *AM. J. OBST. & GYNEC.* 32: 155, 1936.

1420 WEST ERIE AVENUE.

## MESODERMAL MIXED TUMORS OF THE UTERUS

EDWARD C. H. SCHMIDT, PH.D., M.D., AND RICHARD B. SCHUTZ, M.D.,  
KANSAS CITY, MO.

*(From Departments of Pathology, and Obstetrics and Gynecology, St. Luke's Hospital)*

**T**UMORS composed of a variety of tissues are not uncommon in many locations in the body, such as mixed tumors of the salivary glands and embryonal sarcomas of the urinary tract. However, mesodermal mixed tumors of the uterus are rare, only ninety-four having been reported up to 1941, and in more recent years several comprehensive reviews of mesodermal mixed tumors have appeared.<sup>2, 5-12</sup> The first of these tumors was described by Wagner in 1854. Recently, two tumors which appear to be mesodermal mixed tumors of the uterus were encountered in this hospital: one was a small myxomatous cervical growth, and the second a large, bulky, widely extended tumor of the fundus.

**CASE 1.**—A 22-year-old, white, single, nulliparous woman when first seen was complaining of irregular menstrual periods with a somewhat increased flow for the past six months. Prior to this she had had no menstrual irregularity. Lately, the periods occurred every twenty-eight to thirty-five days with four to seven days of bleeding at each time, and the flow had been moderately profuse. On several occasions during the past three months, she had slight intermittent intermenstrual spotting. The urinalysis was normal and the blood count was hemoglobin 15 Gm. per 100 c.c., red blood cells 4,800,000, white blood cells 8,600, coagulation time three minutes. The Kline and Wassermann tests were negative. Vaginal examination revealed a round nodule approximately 1 cm. in diameter, which was firm and superficially lobulated. The attachment to the anterior lateral portion of the cervix was nearly the width of the tumor. The epithelium covering the tumor was less pink than the surrounding epithelium, and there were small superficial blood vessels over the surface. At operation, the base of the tumor mass was removed with a wide excision. The cervix was dilated and the uterine cavity curetted with a moderate yield of endometrium.

The block of cervix measured 8 by 10 by 25 mm. Part of the epithelial surface was smooth and glistening. Projecting above this uniform surface for approximately 3 mm. was a circular area 1 cm. in diameter which appeared to be composed of small rounded projections somewhat like a miniature bunch of grapes. The cut surface below this roughly granular area was firm and had a light gray homogeneous appearance.

Microscopic examination of the cervical biopsy disclosed a peculiar myxomatous infiltration beneath the cervical epithelium. This growth was seen invading the connective tissue of the cervix in all directions, and was even invading into and around the glands. It had broken through the surface epithelium in several areas, forming small papillomas in one location. The stroma was a fibrillary semimyxomatous material which extended into the fibrous elements of the cervix and separated them in many places. The normal cervical structures were completely replaced by the tumor over areas as large as a low-power field. The most prevalent cell was a large cell with long processes extending in several directions. Some were star shaped with four or five long arms extending through the stroma; others appeared to have only one or two long arms. These cytoplasmic elongations were occasionally three to four times the diameter of the body of the cell, and could be seen best in the phosphotungstic acid hematoxylin stained preparations. Those from cells in the same field often interlaced, forming a loose network. The myxomatous stroma did not stain for mucin, but in slides stained by the Masson method it appeared to be composed of very minute granules arranged in long strands interlacing at many points so as to form a fine network. A few cells were roughly oval with one end flattened. In these cells the nucleus was in midposition,



usually filling the breadth of the cell. The cytoplasm was clear except for small dark granules which occasionally appeared to be arranged in lines or rows near the ends of the cells. A few multinucleated giant cells were present, some of which had two to five nuclei along the periphery of the cell, as can be seen in primitive striated muscle cells. Several giant cells had vague cross striation which suggested myoblasts, but striated muscle was not demonstrated although special stains were performed. Other giant cells had a clear cytoplasm, usually with two nuclei in the central portion. It was felt that this constituted a malignant invasive tumor which extended beyond the edges of the biopsy and which would probably be radioresistant. Therefore, a complete hysterectomy was advised.

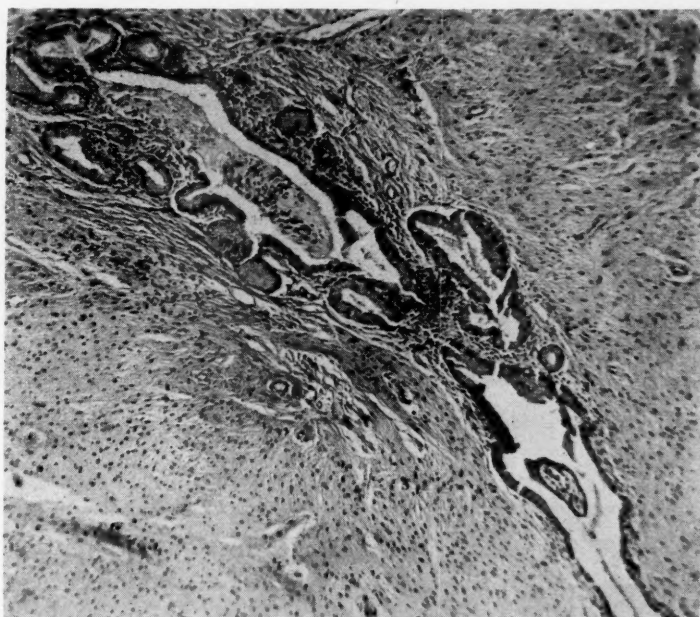


Fig. 1.—Case 1. The tumor can be seen surrounding and invading the tip of a cervical gland.

At operation the uterus was retroflexed and multiple petechiae were scattered over the anterior peritoneal reflection. No extension of the tumor was seen at operation and a wide excision of the cervix and vagina was performed.

The gross specimen consisted of a uterus with cervix and vaginal cuff. There was a small indented area on the anterior portion of the cervix. Section through this point showed a pink tissue extending into the usual pale fibrous tissue. Many small cysts 4 mm. in diameter were present in the cervical canal. The uterine cavity measured 6.5 cm. The endometrium measured 4 mm. in thickness and was pale and smooth except for a soft polyp measuring 18 by 9 by 3 mm. hanging from the fundus. The myometrium showed no abnormalities.

Microscopic sections through the cervix in the region of the puckered scar showed a peculiar type of diffuse edematous fibrillary hyalinization with partial squamous covering. This myxomatous tissue could be seen extending between the fibrous bundles of the cervix. These extensions of the tumor were composed of the myxomatous stroma with few cells. The portion of the tumor remaining in the cervix was quite deep, and in only one area was it near the surface. In some areas numerous fibrillary nerve bundles were seen.

The patient has remained in good health without evidence of recurrence, and is well one year after operation

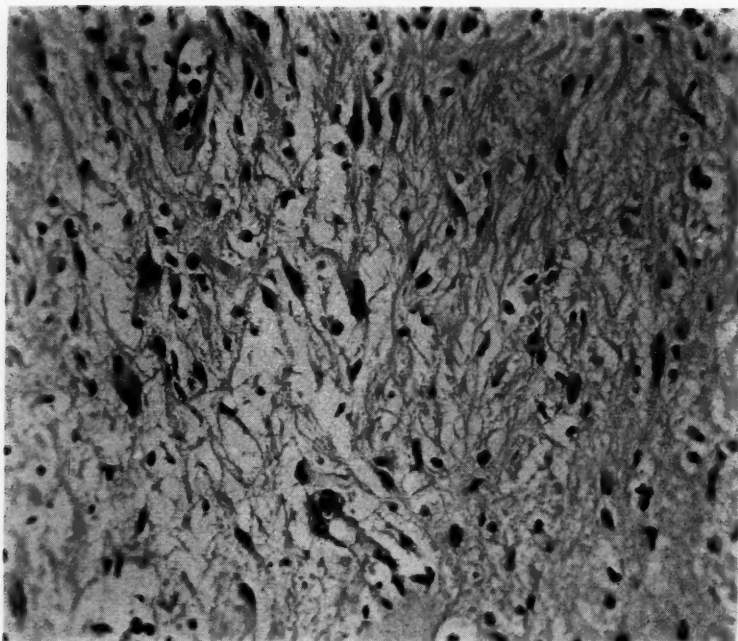


Fig. 2.—Case 1. Stromal elements showing elongated cytoplasmic processes and occasional giant cells.

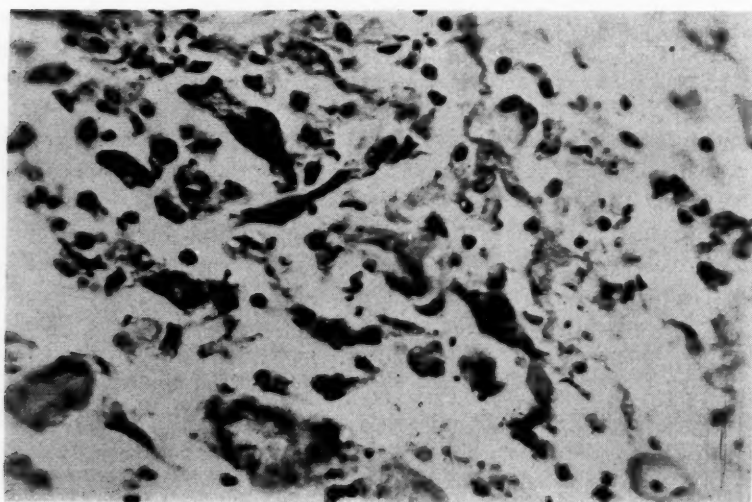


Fig. 3.—Case 1. An area with several multinucleated cells, the cytoplasm of the large cell in the upper left hand portion has darkly staining areas suggesting early cross striations.

CASE 2.—The second case was a 76-year-old white parous woman who was admitted to the hospital complaining of slight vaginal bleeding of twenty days duration. This was of sudden onset and was completely painless. In 1939 she was treated for nephritis and cardiac decompensation. After a prolonged hospital stay she was markedly improved and remained fairly active until her present illness.

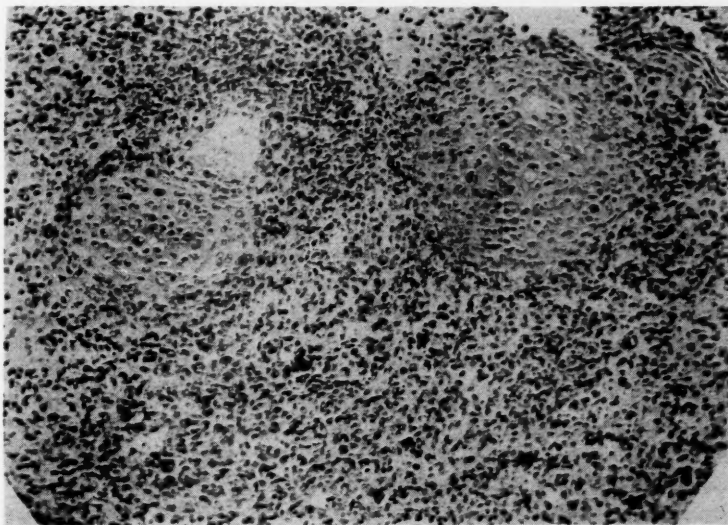


Fig. 4.—Case 2. A focus of cartilage in the midst of the primitive stroma.

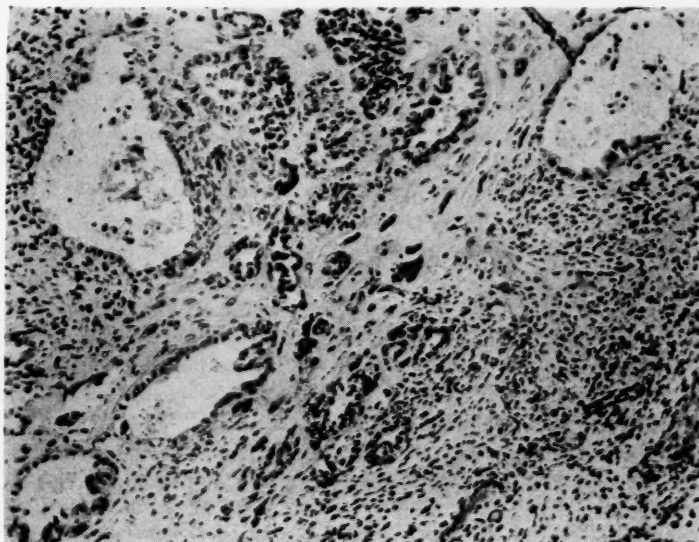


Fig. 5.—Case 2. Glands lying deep in the tumor. Some of the lining cells resemble the cells seen in the Wolffian duct.

Physical examination disclosed an accentuated second sound at the pulmonary and aortic areas, although the heart was not enlarged. Vaginal examination revealed a soft movable mass attached to the cervix. This was rounded, nodular and rubbery, and small

particles broke free easily. The uterus was enlarged by irregular nodulations on the anterior surface. Voided urine showed a trace of albumin. The hemoglobin was 11 Gm. per 100 cubic centimeters. The red blood count was 3,500,000, and the white blood count 10,400. The nonprotein nitrogen, blood chlorides, and blood sugar were within normal limits. The erythrocyte sedimentation rate was 25 mm. per hour.

A dilatation and curettage yielded large quantities of friable white, yellow, and red material which contained minute hard nodules. This was diagnosed as being an unusual malignant tumor, and total hysterectomy and bilateral salpingo-oophorectomy were performed. At operation a tumor of soft friable tissue of varied color was found extending into both broad ligaments and into the pelvic fascia beneath the bladder.

The specimen consisted of a uterus measuring 8 by 7 by 6 cm. The serosa over the fundus was smooth and glistening. However, in the region slightly posterior and inferior to the right broad ligament, there was a small soft yellowish papillomatous body measuring 18 by 13 by 6 millimeters. The lower portion of this was blood stained. Anterior to the right broad ligament, there was a finely granular area in the serosa. The whole uterus felt quite soft and boggy. Protruding from the cut end of the uterus was a soft, necrotic appearing, blood-stained mass. When opened, the uterine canal measured 6 cm. in length. The myometrium measured approximately 8 mm. in thickness. The remainder of the specimen consisted of soft, friable, variously colored tissue which ranged from a slate gray through yellow to red and brown. There was one large mass in the center which was polypoid and 6 cm. in diameter. It was this mass which presented from the uterine os. When this was reflected, the remainder of the tissue was made up of polypoid soft masses which varied in size from small, raised, rounded nodules a few millimeters in diameter to larger ones which measured 4 by 2 cm. in area and were raised 1.5 centimeters. Throughout these nodules, there were occasional firm round foci which measured a few millimeters in diameter. In other portions there were fairly extensive gelatinous areas between the large papillary bodies. In one place near the os there was a firmer area which felt and appeared to be composed of small cartilagenous nodules in a myxomatous stroma. On cut section the tumor masses were pale, soft, and variously colored. These ranged from red through yellow to white. On section through one portion a small quantity of clear fluid flowed forth from numerous oval-shaped cysts measuring 11 by 5 millimeters. Section through the yellowish body presenting at the cervix showed a pale orangish surface, and in the center it was soft and composed of alternate minute yellow and red areas. Each of the tubes measured 5 cm. in length. Through the base of one there was a rather firm area which was indistinctly outlined in the broad ligament. On the other tube there was beneath the serosa a small yellowish nodule measuring 8 mm. in its greatest diameter.

Microscopic examination of the uterine tumor showed a highly undifferentiated spindle and oval cell growth with wide areas of pseudocystic change and some areas of necrosis. The cells varied considerably in size. Some large hyperchromatic deformed nuclei and mitotic figures were also observed. Scattered throughout this tissue were small islands of anaplastic cartilage or cartilage-appearing material which showed a pink or bluish pink homogeneous matrix enmeshing anaplastic cells resembling chondroblasts. Several small islands of fairly well-developed cartilage were scattered through the tumor. The small islets of primitive cartilage and chondroblasts were near these adult cartilagenous centers. Other portions were composed of a myxomatous stroma which did not stain for mucin with either mucicarmine or thionin, but with phosphotungstic acid hematoxylin and Masson stain appeared as a fine network with many minute granules appearing throughout.

There were glandular areas present. These varied from simple cystic structures which were lined by low cuboidal epithelium to narrow glands in which the epithelium was columnar and even clumped in small papillations. Some of these resembled endometrial glands, but others lined by flat epithelium did not. This tumor was classified as a mesodermal mixed tumor, although the possibility of a highly anaplastic teratoma with sarcomatous elements was also considered.



### Histogenesis

It is difficult to explain how a complicated tumor of embryologic structure should occur in different sites in the uterus. Basically, there are two schools of thought to explain this phenomenon: one by metaplasia or disturbance of development of the normal uterine components; the other by embryonal rests or latent anlagen which suddenly start growing under a stress of the organism.

Earlier writers were prone to accept metaplasia or degeneration of a specific uterine tissue as the origin of these tumors. Later writers tend to believe that in the complicated mixed tumors the question of metaplasia cannot be seriously considered because the many components and the embryonal character of the tissues indicates that the origin is due to individual primitive cell or mass tissue transplantation. Wilms was of the opinion that one particle of undifferentiated tissue had been transplanted, and from this anlage developed the most different formation. In mixed mesodermal tumors of the uterus this is thought to be a bit of the Wolffian duct, which must arise from caudad to kidney as no renal elements are found in these tumors, and migrates backward along the course of the ducts. The possibility that these tumors, found in the uterus and cervix, arise from the Wolffian duct is enhanced by Meyer's<sup>13</sup> discovery of a Gartner duct in the uterine wall and the cervix of an adult. His later studies revealed a high incidence of Wolffian elements in the uterus. In a recent study Huffman<sup>14</sup> found remnants of Wolffian ducts in approximately 1 per cent of cervixes studied by serial section.

Our attention was called to these tumors by Case 1 which aroused considerable interest both as to histologic diagnosis and as to prognosis. We have been unable to find any case in the literature where the diagnosis was made from an apparently routine biopsy without enlargement of the cervix or uterus. The biopsy was taken in an attempt to find the cause for uterine bleeding, although later examination revealed an endometrial polyp as the cause of the bleeding. It is interesting that almost 25 per cent of the cervical tumors reported by Meikel occurred at approximately 22 years of age, whereas the range is from 1 to 50 years of age. The minute size of this tumor leads to the belief that the growth may represent the earliest stages in the development of these tumors. The embryonic mesenchyme found in this tumor appeared to be the same as that described in the larger more complex tumors. This neoplasm had begun to develop a botryoid form, and in several areas it resembled microscopically the larger botryoid sarcomas of the cervix. Numerous authors have emphasized the difficulty in determining their malignant nature, and even at microscopic examination this may go undetected. One case (15) reported in 1939, had a recurring cervical polyp removed three times within ten months before its malignant nature was noted.

The second case is characteristic of uterine mixed tumors of the fundus both as to symptoms and as to pathology. Uterine bleeding, brownish foul discharge, and uterine pain or enlargement are the usual presenting complaints in tumors of the body of the uterus. These fundic tumors occur most frequently in the fifth decade of life; over 50 per cent of the reported cases were found in persons in this decade. The mixture of many tissues, all of which can arise from the mesoderm, including myxomatous tissues, cartilage and pseudocartilage and glandlike elements of a difficult nature to identify as to origin, is typical of these mesodermal tumors. The tubelike spaces in our tumor at first led to the diagnosis of a teratoma. Later these glands were taken to be inclusions of endometrial glands. However, the lining of some of the glands in this tumor was part flat cuboidal and did not resemble the lining of the endometrial glands, but did resemble the lining of the embryonic Wolffian duct. This patient began having a foul, blood-tinged discharge approximately ten weeks after operation. This increased gradually but the patient remained fairly active for five months after operation, at which time she became quite ill and died in another city two weeks later.

### Prognosis

A review of the outcome of reported cases indicates that little has been accomplished in treating these tumors. All attempts at therapy have been futile. Radium and x-ray

therapy have not been used extensively, despite the fact that the embryonal appearance of the tumor would lead one to believe that many of them would be radiosensitive. Total hysterectomy appears as the logical treatment if a wide excision of the surrounding tissues is accomplished. Meikel<sup>2</sup> suggested that this be followed by deep x-ray therapy, as a prophylactic against local recurrence or as a palliative measure. Shaw<sup>9</sup> summarized the cases he reviewed by stating "The malignancy is extremely high and I can find no record of a patient recovering any length of time after removal of the growth. In most cases death rapidly follows operation."

Since our first case is apparently the smallest mixed tumor reported, we look forward to a more optimistic future than one would anticipate from a review of the reported cases. In this case, the tumor remained localized within the cervix of the uterus, and no evidence of extension could be found at operation. A case of multiple papillary hydropic tumors of the cervix and cervical stump occurring over a period of seven years with multiple operations, is described by Backer and Minich.<sup>16</sup> When total hysterectomy was performed five months before death, a mixed tumor was found. The authors believed the tumors were parts of the same growth, despite the fact that the specimen from the first operation was not examined histologically. This appears to be the longest clinical course described.

### Summary

1. Two cases of mesodermal mixed tumor of the uterus are reported: one a tumor of the fundus of the uterus with typical findings; the other a minute cervical neoplasm discovered incidentally by biopsy during a dilatation and curettage for uterine bleeding.

2. The cervical tumor was smaller than any other such tumor found in a review of the literature and therefore the prognosis appears good despite the gloomy outlook obtained from reports of other cases.

3. The discovery of an unusual and malignant tumor while still quite small again emphasizes the necessity for microscopic examination of all irregular areas of the cervix.

The authors wish to thank Dr. Ferdinand C. Helwig for his guidance and suggestions, and Dr. Lawrence P. Engel for permission to present the second case.

### References

1. Glass, M., and Goldsmith, J. W.: *AM. J. OBST. & GYNEC.* 41: 309, 1941.
2. Meikel, G. J.: *J. Obst. & Gynaec. Brit. Emp.* 43: 821, 1936.
3. Thiede, M.: *Ztschr. f. Geburtsh u. Gynäk.* 1: 460, 1877.
4. Pick, L.: *Arch. f. Gynäk.* 46: 191, 1894.
5. Robertson, A. R.: *J. Med. Research* 20: 297, 1909.
6. Glynn, E., and Bell, W. B.: *J. Obst. & Gynaec. Brit. Emp.* 25: 1, 1914.
7. Nicholson, G. W.: *Guy's Hosp. Rep.* 69: 173, 1918.
8. Perlstein, I.: *Surg., Gynec. & Obst.* 28: 43, 1919.
9. Shaw, W.: *J. Obst. & Gynaec. Brit. Emp.* 35: 498, 1928.
10. Lochrane, C.: *Proc. Roy. Soc. Med.* 26: 1429, 1933.
11. Lebowich, R. J., and Ehrlich, H. E.: *Surgery* 10: 411, 1941.
12. Lawer, A.: *Beitr. f. Path. Anat. u.z., allg. Path.* 38: 176, 1905.
13. Meyer, R.: *Ztschr. f. Geburtsh u. Gynäk.* 42: 526, 1900.
14. Huffman, J.: *Am. J. Obst. & Gynec.* 56: 23, 1948.
15. Duggan, A. R. H.: *M. J. Australia* 1: 612, 1939.
16. Backer, J., and Minich, K.: *Beitr. z. Geburtsh u. Gynäk.* 10: 532, 1906.

## PEPTIC ULCER IN PREGNANCY

J. BERNARD BERNSTINE, M.D., AND M. H. F. FRIEDMAN, Ph.D.,  
PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Obstetrics Division and the Department of Physiology, Jefferson Medical College and Hospital)

**A**BUNDANT evidence in medical literature shows peptic ulcer in the adult to be predominantly a disease of the male. Before puberty, the reported cases are distributed almost equally between the sexes.<sup>1</sup> After puberty, peptic ulcer occurs considerably more frequently in the male. Various authors have estimated the ratio of its distribution to be from 2 to as high as 4 males per female affected.<sup>2, 3, 4</sup> The mortality statistics of the United States for 1937-1938 showed the sex ratio for duodenal ulcer to be 3.6 males per female.<sup>5</sup>

The reason for the lower incidence of peptic ulcer in women is not known, nor has a satisfactory explanation been advanced for the observation that it is in general a milder<sup>6</sup> and also less fatal disease in women.<sup>7</sup>

Two distinctive features characterize peptic ulcer in the adult woman: (1) it is a relatively uncommon complication of pregnancy, and (2) all symptoms incident to it are ameliorated or abolished upon the advent of pregnancy. The rarity of peptic ulcer during pregnancy has been cited by several authors.<sup>8, 9, 10</sup> Reviewing 70,310 consecutive pregnancy hospital admissions, Sandweiss et al.<sup>2</sup> found only one woman with active symptoms of ulcer. This finding is in sharp contrast to the common occurrence of other diseases of the gastrointestinal tract during pregnancy, such as appendicitis,<sup>11</sup> ulcerative colitis,<sup>12</sup> and cholecystitis.<sup>13</sup> That pregnancy exerts a beneficial effect on ulcer symptoms is well known. Sandweiss et al.<sup>2</sup> reported 52 pregnancies in 25 women proved to have had peptic ulcer. During pregnancy, their ulcer symptoms disappeared in all but one case. To date, only 15<sup>14, 15</sup> authentic cases of duodenal ulcer proved by autopsy have been reported during pregnancy. Although peptic ulcer complicating pregnancy is not a frequent occurrence, we have encountered several cases of it, but only after careful questioning and examination. Very often the ulcer symptoms are either masked or confused by the pregnancy, and therefore missed.

Pregnant women with no ulcer histories have been treated successfully with progesterone to prevent threatened abortion. Recourse to progesterone therapy might therefore be expected in cases of potential abortion during the pregnancy of women with histories of peptic ulcer. This treatment has actually been adopted on three occasions with distinctly drastic results.

These three cases together with a review of one in the literature<sup>16</sup> appeared of sufficient interest to warrant reporting, since, to our knowledge, no mention has previously been made of the ulcer-aggravating effects of progesterone on pregnant women with histories of peptic ulcer prior to pregnancy.

### Report of Cases

**CASE 1.**—Patient D. McK., white, aged 38 years. Menstrual history. Onset at 15 years of age, every 28 days for seven days, no pain. This patient had infantile paralysis at the age of 4 years and made a good recovery. In 1936 she suffered from "indigestion."

In 1937, this patient had an attack of hematemesis, and at times noticed tarry stools. Several attacks of hematemesis followed. The patient said she was hospitalized and placed on a milk and cream diet. She remained in hospital for three weeks; following this treatment, she returned home and was treated by her family physician for peptic ulcer and anemia. It took her six months to regain her normal status and return to work.

In May, 1942, she was delivered spontaneously, at 7½ months, of a macerated, stillborn male child; and, despite careful studies, no apparent cause could be found in either parent or child. During this gestation period the patient was free from ulcer symptoms.

In October, 1943, she again became pregnant. Progesterone therapy was considered advisable and was therefore instituted. The pregnancy progressed satisfactorily until the 7th month of gestation. At that time the patient complained of feeling faint; when she moved her bowels, the stool was copious and very tarry. Immediately afterwards, she vomited large amounts of coffee-ground material. Her symptoms were strongly suggestive of peptic ulcer. She was put to bed and transferred to the hospital where she was placed on an ulcer diet, and given vitamin K. She remained in bed six weeks prior to delivery, receiving several blood transfusions. She was delivered at term, July 23, 1944, of a normal, living, female child weighing 6 pounds 6½ ounces. She made an uninterrupted recovery from labor. Over a year later, she was apparently doing satisfactorily.

In October, 1944, she was x-rayed, and, although the ulcer could be visualized, she offered no complaints and at this date is feeling well.

CASE 2.—Patient C. B., white, aged 28 years. Menstrual history, onset at 12 years of age, every 28 days, for four or five days, no pain. This patient had the usual childhood diseases and no other illness of importance.

In January, 1939, the patient had a spontaneous abortion at 6 to 8 weeks.

In September, 1939, she had a spontaneous abortion at 4½ months. Following this abortion, the patient complained of symptoms suggesting ulcer. She was x-rayed, and peptic ulcer was diagnosed. She was placed on an ulcer diet and given medical treatment. Prompt response resulted in a twenty-pound weight gain. She came under observation again on July 9, 1940. At that time, examination revealed a six weeks' pregnancy. Physical examination was essentially negative. There were absolutely no ulcer complaints. Due to her previous obstetric history (two abortions), it was considered advisable to institute rest and progesterone therapy. Proluton was administered until the fourth month of pregnancy. At that time the patient had an attack of hematemesis, coupled with severe heartburn and a recurrence of ulcer symptoms. Vomiting persisted; the urine showed albumin and hyaline casts and acetone. During this period, the patient had several attacks of hematemesis. About one month later, she was delivered of a stillborn child; then followed a long convalescence. Throughout the entire pregnancy, both ulcer diet and treatment were maintained as before conception.

CASE 3.—Patient A. T., white, aged 26 years. Menstrual history, onset at 14 years of age, every 28 days for 5 days.

She was delivered of a male child Nov. 14, 1936, low forceps, moderate postpartum hemorrhage.

In October, 1939 she had a gastroenterostomy for peptic ulcer.

She last menstruated July 5, 1942. In September, 1942, following a threatened abortion, the patient was ordered rest and sedation. On Nov. 5, 1942, the abortion symptoms recurred, and progesterone was prescribed, resulting in a gradual improvement in the patient's condition.

*Gastric Analysis, Dec. 7, 1942.*—

*Macroscopic:* Large amount of mucus in residue.

*Microscopic:* Many pus and red blood cells and epithelial cells.

Report:	Blood	Free Acid	Total Acid
	+	-	6
	-	28	41
	-	37	53

In March, 1943, she complained of nausea, vomiting, and melena. The same month she was delivered spontaneously of a premature living male child.

CASE 4.—Dr. Edward B. LeWinn's<sup>16</sup> patient, white, aged 35 years. Menstrual history, onset at 13 years, every 28 days for four or five days, gravida ii.

This patient had a history of epigastric pain in 1930, and an appendectomy was performed in 1931. Her symptoms were not relieved. In 1938, she had a cholecystectomy, result-



ing in a temporary relief of her symptoms. She was then put on a course of nonsurgical biliary drainage. In April, 1945, she had a spontaneous abortion at six weeks. Her last menstrual period was July 27, 1945, her expected date of delivery May 2, 1946.

In view of this patient's history of previous abortion, she was maintained on progesterone throughout the present pregnancy. On March 18, 1946, the patient experienced epigastric discomfort about one to one and one-half hours after the ingestion of food. Her symptoms progressed, and she later noticed tarry stools and blood in the vomitus. On April 12, 1946, she suffered severe gastrointestinal hemorrhage; blood transfusions were repeatedly administered, and the patient was very ill. On April 17, 1946, there was a slight improvement in her condition, and on April 19, she was delivered of a stillborn, premature, macerated male child. On May 2, 1946, a fractional gastric analysis was made, and on May 3, x-ray examination showed evidence of peptic ulcer.

### Discussion

A review of the literature reveals that duodenal ulcer occurs less frequently in women than in men and that it is a rare complication of pregnancy. In women known to have had peptic ulcer, its symptoms almost always disappear with the advent of pregnancy.

In the three cases reported of ulcer occurring during pregnancy, the history of each patient suggested or proved the existence of an ulcer prior to pregnancy. The ulcer symptoms abated during the early stages of the pregnancy in all three women; yet the later administration of progesterone was followed in each case by an aggravation of the ulcer, by hemorrhage, and a stormy course almost terminating fatally.

The relationship between sex and incidence of peptic ulcer has led several investigators to place peptic ulcer on an endocrine basis, and to attempt a sex hormone therapy. On the whole, the results of these investigations have been inconclusive. Among the sex hormones used for the treatment of peptic ulcer in the human being are included: estrogens,<sup>17</sup> ovarian follicular hormones,<sup>18</sup> estrones,<sup>19</sup> and urinary chorionic gonadotropins.<sup>20</sup>

Experiments conducted on dogs with surgically induced duodenal ulcers and on men with peptic ulcer have shown the administration of human pregnancy urine extracts to have a beneficial effect on the ulcer. Thus, in dogs with experimental Mann-Williamson ulcers, daily injections of extracts of pregnancy urine reduced the incidence of perforation from 72 per cent to 20 per cent and increased over-all benefits from 10 per cent to 85 per cent. While this would suggest that urinary gonadotropins have an antiulcer effect, the picture is unfortunately not at all clear. Recent work has shown the anti-ulcer factor to be present not only in the urine of pregnant women, but in the urine of non-pregnant women and men as well.<sup>20</sup>

The relationship between progesterone and gonadotropin is such as to indicate possible antagonism between them. The reported beneficial effects of gonadotropin on peptic ulcer would suggest the adverse action of progesterone. Whether the respective actions of gonadotropin and progesterone affect the lesions directly or indirectly is not clear at the present time.

The history of peptic ulcer should place the obstetrician on guard when considering the application of progesterone against threatened abortion. We may further suggest that the incidence of peptic ulcer in pregnancy, while

admittedly not common, occurs perhaps more frequently than hitherto credited. In ulcer patients, its symptoms are said to abate during the first trimester of pregnancy. Consideration should be given to the possibility that, in some cases, peptic ulcer during the first trimester may be masked by, or misdiagnosed as, hyperemesis gravidarum. Indeed, this suggestion is supported by Mussey of the Mayo Clinic, who reports that of 370 necessary operations during pregnancy, over a period of ten years, two were for peptic ulcer.

To our knowledge, no reports have been published establishing progesterone as an ulcerogenic agent. In the normal nonpregnant and pregnant subject, it would appear not to react on the gastrointestinal tract. Only when an ulcer lesion is or has been present are the aggravating effects of progesterone evident. It would be interesting to determine whether administration of progesterone to a nonpregnant ulcer patient would engender the deleterious effects observed in the pregnant ulcer patient.

### References

1. Saltzstein, H. C., Farbman, A. A., and Sandweiss, David J.: *Endocrinology* 27: 400, 1940.
2. Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: *Am. J. Digest. Dis. & Nutrition* 6: 6, 1939.
3. Eusterman, G. B., and Balfour, D. C.: *The Stomach and Duodenum*, Philadelphia, 1936, W. B. Saunders Company.
4. Ivy, A. C.: *J. A. M. A.* 132: 1053, 1946.
5. Bureau of the Census, United States Department of Commerce, *Mortality Statistics for 1920-1945*.
6. Winkelstein, A. J.: *Mt. Sinai Hospital* 12: 773, 1945.
7. Metropolitan Life Insurance Company Bulletin 26: 9, 1945.
8. Adair, F. L., and Steiglitz, E. J.: *Obstetric Medicine*, Philadelphia, 1934, Lea & Febiger.
9. Szenes, A. Mitt. A.D. Grenzgeb, D. U. Chir. 37: 652, 1924. (Cited by Anderson, 1942, ref. No. 15.)
10. Mulsow, F. W., and Brown, W. E.: *AM. J. OBST. & GYNEC.* 31: 1041, 1936.
11. Twyman, R. A., Mussey, R. D., and Stalker, L. K.: *Proc. Staff Meet. Mayo Clin.* 15: 484, 1940.
12. Bargaen, J., Arnold, Nunex, Calixto Jose, and Mussey, Robert D.: *AM. J. OBST. & GYNEC.* 38: 146, 1939.
13. Biskind, Leonard H., and Pevaroff, Herschell H.: *Ohio State M. J.* 38: 1013, 1942.
14. Sandweiss, D. J., Podolsky, H. M., Saltzstein, H. C., and Farbman, A. A.: *AM. J. OBST. & GYNEC.* 45: 131, 1943.
15. Anderson, G. W.: *AM. J. OBST. & GYNEC.* 43: 883, 1942.
16. LeWinn, E. B.: *AM. J. OBST. & GYNEC.* 54: 114, 1947.
17. Friedlaender, W.: *Arch. urug. de med. cir. y. especialid.* 28: 231, 1946.
18. Arpino, G.: *Folia Med.* 24: 85, 1938.
19. Abrahamson, R. H., Church, R., and Hinton, J. W.: *Am. J. M. Sc.* 204: 809, 1942.
20. Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., and Saltzstein, H. C.: *Am. J. Digest. Dis. & Nutrition* 8: 371, 1941.

## VAGITUS UTERINUS IN TWIN PREGNANCY

### With Prolapsus Funis and Its Treatment Under Continuous Caudal Analgesia

JOSEPH G. CROTTY, M.D., F.A.C.S., AND LEONARD W. KUEHNLE, M.D.,  
CINCINNATI, OHIO

(From the Obstetrical Service of the Good Samaritan Hospital)

**V**AGITUS uterinus, or the audible crying of the fetus in utero, is an unusual phenomenon of pregnancy first described in the literature by J. B. von Fischer in 1730<sup>1</sup> and renowned in legend and fable centuries before, Mahomet and St. Bartholomew having been said to have made themselves heard from the womb before birth.<sup>2</sup> Numerous such cases have been reported in the literature, and, in 1943, Ryder<sup>3</sup> reviewed 123 authentic cases occurring between 1800 and 1941, including his own. Since 1941, a number of other cases have been cited, notably the observations of Thorp,<sup>4</sup> Bourgeois and King,<sup>5</sup> Mitchell,<sup>6</sup> Kitzmiller and Mitchell,<sup>7</sup> Rucker,<sup>8</sup> and M. A. Lewis.<sup>9</sup> Kitzmiller and Mitchell,<sup>7</sup> as well as DeLee,<sup>2</sup> emphasize the necessity of fulfillment of the following conditions before intrauterine crying is possible: (1) The membranes must have ruptured. (2) There must be some manipulation to stimulate the fetus. (3) Air must enter the uterus, or this last requirement may be satisfied by the production of gases within the uterine cavity. It is noteworthy that the cases reported by Thorp, Rucker, and Lewis, like the one herein presented, were conducted under caudal analgesia, while that of Mitchell also involved prolapse of the umbilical cord.

### Case Report

This patient was a 34-year-old white woman who had previously had three normal deliveries. At the seventh month, a diagnosis of twin pregnancy was confirmed by x-ray. On the morning of Aug. 14, 1947, at full term, the membranes ruptured at home, and, shortly thereafter, her physician-husband noted that the umbilical cord was protruding from the vagina. She was immediately hospitalized, where it was observed that the prolapsed cord was still pulsating normally. The patient was not in labor and there were no uterine contractions. Continuous caudal analgesia was induced at once, using 1.5 per cent Metycaine administered by the technique of Hingson and Edwards.<sup>10</sup> As soon as analgesia was complete and the blood pressure stabilized, the patient was placed in the knee-chest position (Fig. 1) and the vulva and perineum surgically prepared and draped. Inspection now revealed that a foot, as well as the cord, was lying in the vagina. The cervix was thick and admitted only three fingers. It was grasped with sponge forceps (Fig. 2) and drawn upward as the gloved hand pushed the foot downward into the fundus and replaced the cord much as one might drop a worm into a bottle. It is obvious that during this manipulation the amniotic sac must inevitably have been ballooned up with air by atmospheric pressure (Fig. 2), and thus all of the conditions outlined by DeLee and by Kitzmiller and Mitchell were fulfilled. A large-sized Voorhees bag was now inserted into the uterus and tightly distended with water (Fig. 3), and the patient allowed to resume the dorsal position, the bag preventing escape of the trapped intrauterine air. The air-distended amniotic sac, completely drained of fluid, provided an ideal medium for respiratory movements and for the transmission of sound, oxygen supply to the fetus being still continuously supplied by way of the pulsating umbilical cord.

About one hour after the insertion of the bag, regular uterine contractions began and, after another hour, the patient and observers were amazed to hear the cry of the unborn fetus. This cry was no weak sound, audible only with the stethoscope, but was identical in every way with the wail of a newborn babe and was plainly heard by nurses and doctors all over the room. Crying continued for one and one-half hours until delivery and would follow each uterine contraction. The cervix was now completely dilated and the bag was expelled from the vagina. The first twin, a 5 pound, 11 ounce girl, was delivered by breech extraction, could be

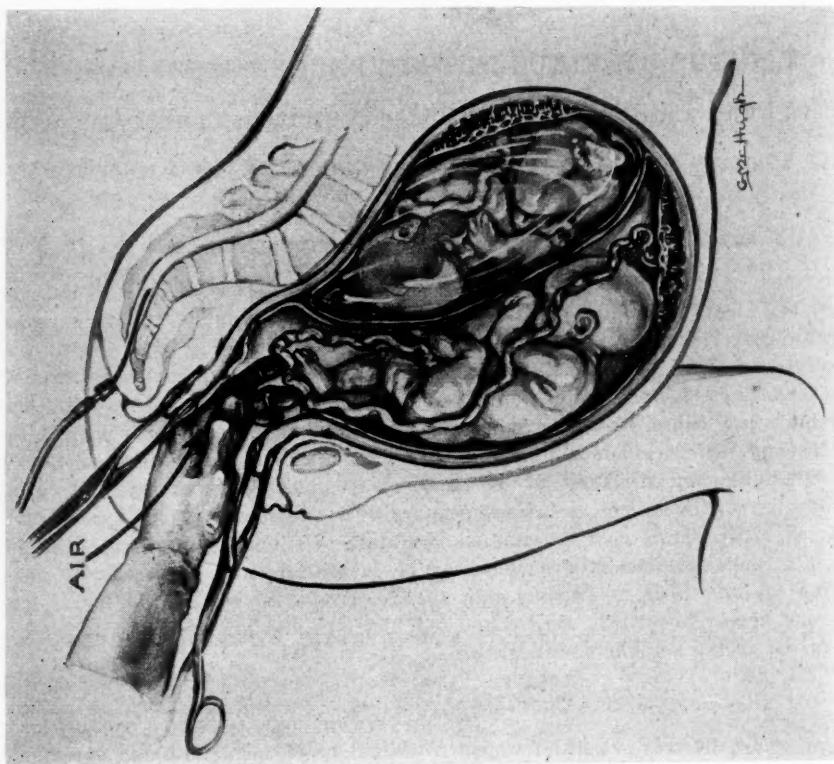


Fig. 2.

Fig. 2.—Illustrates technique of replacement of prolapsed cord in knee-chest position. The cervix is grasped with sponge forceps and upward traction made by assistant; the operator's hand gently replaces cord and foot which are dropped down into uterus much as one would drop "a worm into a bottle." It is obvious that the amniotic sac becomes distended with air during this procedure.

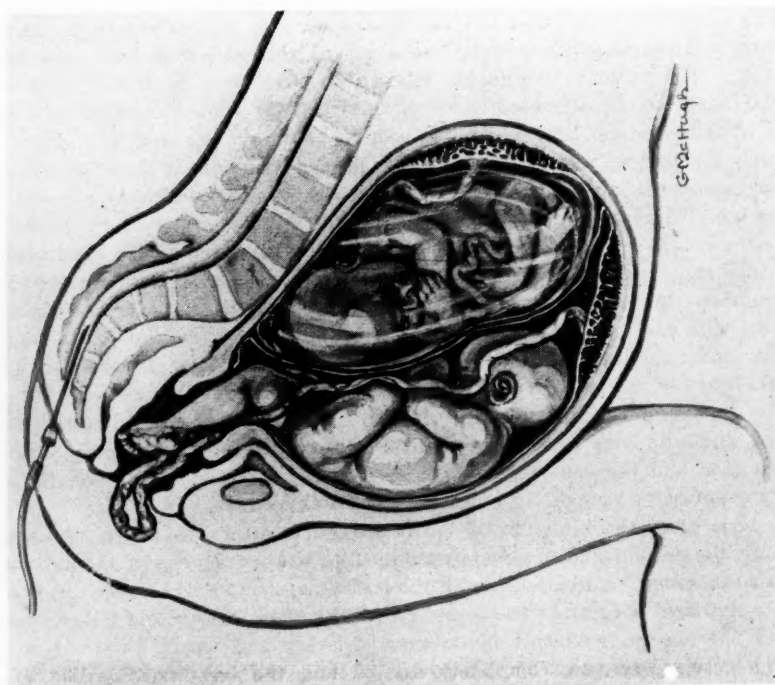


Fig. 1.

Fig. 1.—Shows patient in knee-chest position, needle in caudal canal, footling breech presentation of first twin with prolapse of cord and foot; cervix undilated and uneffaced.



heard crying during the manipulations incident to delivery, and made definite efforts to escape the grasp of the operator during the procedure. The infant was well developed and cried lustily immediately after birth, being none the worse for the experience.<sup>11</sup> The second twin, a 4 pound, 11 ounce girl, was delivered promptly by version and extraction after artificial rupture of the membranes.

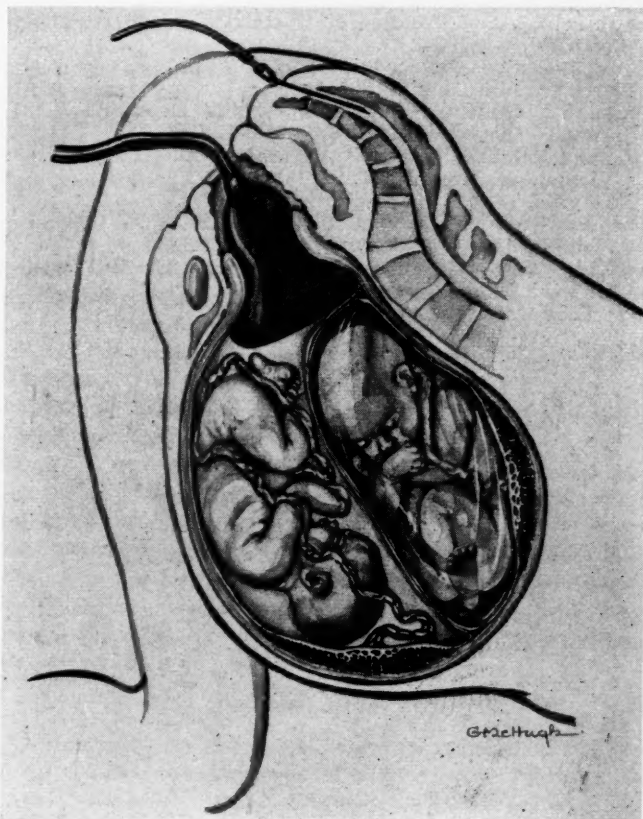


Fig. 3.—Shows large Voorhees bag inserted into uterus and distended with water, preventing recurrence of prolapsus funis, and incidentally "trapping" air in the uterus and continuing the balloonlike distention of the amniotic sac of the first twin.

This case of vagitus uterinus serves to emphasize a number of important facts:

1. Continuous caudal analgesia, as in the cases reported by Thorp, Lewis, and Rucker, apparently made intrauterine crying more likely because the baby was not depressed by sedatives or narcotics; Rucker believes that the condition is destined to become more common with the more widespread use of regional nerve block anesthetics.

2. An often neglected method of replacement of the prolapsed cord is presented, and is obviously made more practical and effective under the conditions of patient cooperation made possible by continuous caudal analgesia, one of us (J. G. C.) having used the method successfully on two previous occasions without any anesthetic agent whatsoever.

3. While vagitus uterinus has classically been considered to be a sign of intrauterine asphyxia, and while in Ryder's collected series of cases the fetal mortality approaches 20 per cent, the conclusions of Peters<sup>12</sup> that "fetal mortality following vagitus uterinus is in practically all cases attributable to mechanical injury suffered by the fetus during the course of ill-advised procedures to effect hasty delivery," seem to be justified. As in every other obstetric emergency, the operative procedure elected should be carefully, intelligently, and deliberately selected. Haste is never indicated!

4. The widespread notoriety given this case in the public press has brought to light a number of similar experiences, hitherto unreported, making it quite obvious that the condition is more common than we have supposed.

### References

1. von Fischer, J. B., quoted by Freed, Frederick: *AM. J. OBST. & GYNEC.* **14**: 87, 1927.
2. DeLee, J. B.: *Principles and Practice of Obstetrics*, ed. 6, Philadelphia, 1932, W. B. Saunders Company, p. 870.
3. Ryder, G. H.: *AM. J. OBST. & GYNEC.* **46**: 867, 1943.
4. Thorp, A. T.: *North Carolina M. J.* **6**: 327, 1945.
5. Bourgeois, G. A., and King, H. L.: *Bull. U. S. Army M. Dept.* **8**: 147, 1947.
6. Mitchell, A. M.: *AM. J. OBST. & GYNEC.* **48**: 547, 1944.
7. Kitzmiller, J. L., and Mitchell, W. B.: *West. J. Surg.* **50**: 620, 1942.
8. Rucker, M. P.: *Virginia M. Monthly* **57**: 28, 1930.
9. Lewis, M. A., Nashville, Tenn.: Personal communication.
10. Hingson, Robert A., Hingson, E., and Lull, Clifford B.: *The Control of Pain in Child-birth*, Philadelphia, 1944, J. B. Lippincott Co.
11. "Heralded Arrival," *Time Magazine* **50**: 8, 49, Aug. 25, 1947, and Associated Press Dispatches of week following Aug. 14, 1947.
12. Peters, Lindsay: *California and West. Med.* **31**: 278, 1929.

136 WEST McMILLAN STREET.

## ADENOCARCINOMA OF THE UTERINE FUNDUS IN IDENTICAL TWINS

JAMES P. PALMER, M.D., AND RAYMOND W. MITCHELL, M.D., BUFFALO, N. Y.

(From the Roswell Park Memorial Institute)

CASES of tumors in twins have always been of interest to geneticists and physicians. In reviewing the literature for the past twenty years we were unable to find a case of uterine fundus carcinoma in monozygous twins. Cerebellar tumors,<sup>1</sup> lymphocytic,<sup>2</sup> and chronic lymphatic leukemia,<sup>3</sup> retinoblastoma,<sup>4</sup> carcinoma of the stomach,<sup>5</sup> carcinoma of the breast,<sup>6, 7</sup> and adenocarcinoma of the large intestines,<sup>8, 9</sup> have been reported in twins. Dr. Madge T. Macklin, Research Associate in the Department of Medicine at Ohio State University, who has done a great deal of work in tumors in twins, states that she does "not know of any other case in which carcinoma of the fundus in each member of an identical twin pair has been reported."<sup>10</sup>

In assuming that these twins were identical, we did not rely on the statements of the patients and family, but made every effort to disprove their identity. The patients were identical in skin coloring, height, weight, and the color of their eyes and hair. Also, they frequently took each other's examinations while in school and only the most intimate members of the family could tell them apart.

In attempting to disprove their identity, Dr. Ernest Witebsky of the University of Buffalo examined their blood and each patient was: Blood Group: A, subgroup A<sub>1</sub>; Rh positive, Subtype Rh<sub>1</sub>Rh<sub>2</sub>; and blood type M.<sup>11</sup>

Furthermore, Professor of Genetics D. C. Rife of Ohio State University examined the fingerprints of these patients and reported that "in this pair there are more than the average degree of differences between right and left hands, and the fact that these differences are as great as those between the two rights and two lefts of the pair suggests that they are probably identical."<sup>12</sup>

### Case Report

The family history of these twins was irrelevant, except for the fact that the mother died of carcinoma of the ovary at the age of 52.

I. F. V., 50-year-old white woman, single, no reported pregnancies. Referred to the Roswell Park Memorial Institute on Jan. 11, 1943. The history included the usual childhood diseases, typhoid fever, influenza, and rheumatic fever. Menstrual history: Menses began at 14 years, occurred every 28 days, lasting 4 to 5 days; occasional back pain with menstrual flow.

*Present Illness.*—The patient first noted pain in the abdomen in November, 1941. In January, 1942, she had intermenstrual bleeding with clotting during the menses periodically until August, 1942, at which time she had profuse continuous bleeding. On Nov. 13, 1942, she had a subtotal hysterectomy for a fibroid uterus. The pathologic report was multiple subserous fibromyomas, submucous fibromyoma, and adenocarcinoma of the corpus uteri. The patient was referred to this institution.

*Physical Examination.*—Thin, nervous, anemic-appearing white woman weighing 115 pounds. General examination essentially negative.

Pelvic examination: no discharge; cervix deformed, feeling slightly nodular on the left posterior; stump of the cervix movable. Blood count: hemoglobin 47%, red blood cell count 3.5 million. Urine: negative.

*Treatment.*—Jan. 11. 6 1-mg. seeds implanted in cervix. Dosage 798 mg. hr.

Jan. 11 to Feb. 2. 200 kv. x-ray to anterior and posterior pelvis for total skin dosage of 3,300 r.

April, 1943. Asymptomatic with no evidence of disease.

August, 1947. Report from a mental institution: hypertension and senile vaginitis with no evidence of recurrent disease.

I. M. V., 55-year-old white woman, single, no reported pregnancies. Referred to the Roswell Park Memorial Institute Aug. 6, 1947.

*Past History.*—Usual childhood diseases and rheumatic fever. Menstrual history: Menses began at 13 or 14 years, occurred every 28 days, lasting 4 to 5 days. December, 1944: Mikulicz operation for lesion of the sigmoid; left salpingo-oophorectomy.

*Present Illness.*—Patient has had metrorrhagia and menorrhagia periodically since 1942. She had a severe hemorrhage in June, 1947, and a dilatation and curettage were done July 5, 1947. Pathologic report was adenocarcinoma of the uterus. Patient referred to this institution.

*Physical Examination.*—General examination was essentially negative. Well-healed lower abdominal scar, no masses palpable. Weight 128 pounds.

Pelvic examination: cervix appeared negative and blood was coming from the external os. Fundus not palpable. Canal measures 3 inches and heavy curettings were obtained with the Novak curette. Possible broad ligament extension on the left but it might be postoperative scarring.

*Laboratory Examination.*—Hemoglobin 70 per cent. Red blood count 3.5 million. White blood count 7,000. Normal differential. Urine, negative. Blood sugar: 106. Non-protein nitrogen, 29. Albumin 3.23. Globulin 2.69. Chlorides 472. Cholesterol 161. X-ray of chest, pelvis, and lumbar spine, negative. Electrocardiogram, sinus tachycardia.

*Treatment.*—August 6, radium tubes 3 by 15 mg. for 133 hours—6000 mg. hr. Readmitted to hospital Sept. 26, 1947. September 30, panhysterectomy performed. Patient discharged in good general condition on Oct. 13, 1947.

It is interesting that in both cases the uterus showed multiple leiomyomas and the adenocarcinoma was anaplastic and showed evidence of muscular invasion. Furthermore, although there was an interval of over four years between admissions of the two patients, their symptoms of irregular bleeding date back to approximately the same time in each case. It cannot be proved, but it is possible, that either a malignant or premalignant condition existed in the second patient at the time of the illness of her sister four years ago.

### References

1. Leavitt, F. H.: Archives of Neurol. & Psychiat. 19: 617-622, 1928.
2. Siegel, A. E.: Atlantic M. J. 31: 748-749, 1928.
3. Dameshek, W., Savitz, H. A., Arbor, B.: J. A. M. A. 92: 1348-1349, 1929.
4. Benedict, W. L.: Arch. Ophth. 2: 545-548, 1929.
5. Militzer, R. E.: Am. J. Cancer 25: 544-550, 1935.
6. Munford, S. A., Linder, H.: Am. J. Cancer 28: 393-396, 1936.
7. Phillips, R. B.: Staff Meet. Mayo Clin. 13: 209-216, 1938.
8. Macklin, M. T.: Arch. Path. 27: 133-137, 1939.
9. Cole, J., Humphrey, H.: Connecticut M. J. 5: 279, 1941.
10. Macklin, M. T.: Personal communication.
11. Witebsky, E.: Personal communication.
12. Rife, D. C.: Personal communication.



## MEIGS' SYNDROME

W. R. WHITEHOUSE, M.D., AND R. W. KIMBRO, M.D., CLEBORNE, TEXAS

**I**N 1937 Meigs and Cass presented histories of four patients who had ascites and hydrothorax associated with fibroma of the ovary. The phenomenon was immediately relieved in each case by the successful removal of the ovarian tumor, and such has been the story with most of the total of 45 cases reported. Each case has demonstrated the important fact that, although the patient presents a picture of hopelessly far-advanced malignancy, a phenomenal cure may be obtained. Apparently, the major limitation is with the knowledge of the doctor who first observes the case.

As in the case seen by us, physicians not including this syndrome in their differential diagnosis are likely to avoid the risk of a possible postoperative mortality, and thus condemn the patient to a slow death resultant from repeated thoracentesis and paracentesis. Successful recovery of each case stands as a monument to the keen observance of the authors of the original communication.

A number of questions remain unanswered, such as the mechanism of production of the probably identical fluid in the pleural and peritoneal cavities. The most likely explanation of the pleural fluid is that the "one way" pathways from abdomen to chest are lymphatics; first by way of the interstices of the cells under the diaphragm, thence to the subdiaphragmatic lymphatics, and thence into the chest.

### Case Report

L. H., aged 48 years, white, para iii, gravida iii, married, was first seen July 12, 1947. The patient complained of extreme dyspnea which had been progressive for one week, having begun at the time she had "intestinal influenza" with diarrhea and fever. She had consulted a doctor who had made a diagnosis of advanced malignancy and had recommended paracentesis. For the two previous years she had noticed a swollen abdomen and a hard mass located in the lower region, which caused no more symptoms than those due to its bulk. The family history, as well as social, medical, and surgical was negative. The menses were scant but regular and she had conducted a normal housewife's existence prior to the relatively acute onset of dyspnea.

*Physical examination* revealed a cachectic, white, sthenic, woman appearing older than her stated age, and laboring for breath. Her weight was approximately 135 pounds; blood pressure 130/85; temperature 102° F., pulse 120 per minute, and respirations 60 per minute, even with oxygen furnished by pharyngeal catheter.

Examination of the chest showed complete flatness to percussion and an absence of breath sounds on the right. By percussion, palpation, and auscultation, the heart was shifted markedly to the left but was irregular only in the rapid rate. The abdomen was protuberant and symmetrically enlarged to the size of a seven months' pregnancy. Shifting dullness in the dependent portion was elicited, as well as a fluid wave. No viscera were palpable; however, a large firm, movable mass, about the size of a seven months' pregnancy filled the lower abdomen.

Clinical evaluation revealed the following:

*Blood Count.*—Hemoglobin 13.2 Gm., red blood cells 3.8 million, white blood cells 14,150, differential normal.

*Blood Sedimentation Rate.*—42 mm. (normal 12 mm.).

*Urine.*—Specific gravity 1.022, albumin 1 plus, sugar negative, microscopic, occasional pus cell.

*Blood Chemistry.*—

Sugar	100	mg./100 c.c.
Nonprotein nitrogen <sup>1</sup>	57	mg. per cent
Serum albumin	4.29	
Serum globulin	2.00	
Total blood protein	6.9	mg. per cent
Wassermann	negative	
Transfusion type	0	

*Chest X-ray.*—Revealed a marked elevation of right diaphragm and right pleural effusion. The heart shadow was shifted markedly to the left and the right lung was completely collapsed.

*Thoracentesis Fluid.*—In eight days of observation, in 3 taps, over 12 L. of fluid were removed. This had a low cell count, chiefly plasma cells, specific gravity of 1.040, and no bacteria grew on guinea pig inoculation or upon prepared media.

On July 30, 1947, with a tentative diagnosis of Meigs' syndrome, and under lumbar spinal anesthesia, the abdomen was opened, to reveal about 2,000 c.c. of straw-colored fluid and a large tumor of the left ovary, firmly embedded in the lower abdomen. Following freeing from a tenaceous exudate, the tumor was removed and the abdomen closed in layers with quilting cotton, without drainage. During the operation, a transfusion of 500 c.c. of whole blood was given, followed by 1,000 c.c. of 5 per cent glucose in normal saline intravenously.

*Pathology.*—Grossly the specimen consisted of an encapsulated, exudate-covered, mass measuring 24 by 20 by 8 cm., weighing 2,800 Gm. The tumor was firm and cut surface showed interlacing bundles of fibers in a grayish stroma.

*Microscopic.*—Sections showed stellate cells with spindle-shaped nuclei, arranged in bundles having an interlacing pattern. No disturbance of uniformity or growth activity was noted.

*Diagnosis.*—Fibroma of the ovary.

Postoperatively, the patient was ambulated as usual sitting at the bedside in twenty-four hours and walking twice daily each day thereafter. The convalescence was uneventful except for a bout of paroxysmal tachycardia on the third postoperative day. Following the reduction to a normal rhythm by rapid digitalization, the patient followed the usual pattern and was sent home on the seventh postoperative day.

A follow-up after two weeks revealed that no fluid could be shown to be present in either chest or abdominal cavity. The patient was feeling quite well and had resumed her normal duties around her home.

It is again emphasized by this, the forty-sixth case reported, that any patient who exhibits the characteristics described and who presents the triad of pelvic tumor, ascites, and hydrothorax should have the benefit of operative exploration, no matter how hopeless the condition may appear.

310 CHAMBERS STREET,  
CLEBORNE, TEXAS.

## BULLET WOUND OF A GRAVID UTERUS WITH INTESTINAL PERFORATION

OTTO R. HOLTERS, M.D., F.A.C.S., AND BENJAMIN DAVERSA, M.D., F.A.C.S.,  
NEPTUNE, N. J.

(From the Fitkin Memorial Hospital)

IT WAS considered advisable to report this case, not only for its interesting potentialities, but also for the paucity of information in the literature.

Mrs. E. J., 31 years of age, 8 months pregnant, gravida iii, para ii, was admitted to the surgical service of the Fitkin Memorial Hospital, at 3 P.M., on Aug. 16, 1947. Shortly before admission, she had sustained three bullet injuries to the body. A bullet wound of entrance was found in the upper right quadrant of the abdomen, with point of exit in the mid left flank, the bullet unquestionably having perforated the uterus. There were two wounds of the lumbar dorsal area of the back which, although bleeding profusely, were considered to be flesh wounds. The left index finger had been fractured by a third bullet injury.

The innocuous external appearance of the injuries belied the serious nature of her general condition. The patient was pale and covered with a cold perspiration; the pulse was rapid, feeble but regular; the blood pressure was 118/64. There was evident apprehension and moderate air hunger. She complained of severe and steady abdominal pain. All the symptoms pointed to internal bleeding with impending shock. The uterus was hard, tense, and exquisitely tender to palpation. The fetal heart was indistinctly heard in the beginning but soon was lost.

The patient was given intensive shock-control therapy, including blood plasma and whole blood intravenously. Under spinal anesthesia, the abdomen was opened through a left paramedian incision, its midpoint being the level of the umbilicus. Upon opening the peritoneum about 300 c.c. of free blood were found in the peritoneal cavity. Examination of the uterus revealed two ragged perforations on the anterior and posterior fundal surfaces, each about 1 cm. in diameter, which were bleeding freely. A classical cesarean section was performed and a stillborn infant delivered. The infant had not been injured by the projectile. The placenta was found free in the fundal area. It had been perforated and separated from its bed by a large retroplacental hematoma. The uterine incision was closed in two layers; the first layer interrupted and the second a continuous Lembert. Both perforations of the uterus were closed with mattress sutures, controlling the bleeding. With the uterus emptied of its contents, it was then possible to explore the abdomen for further injuries. Investigation of the abdominal organs revealed multiple perforations of one segment of the midportion of the ileum. Accordingly, about two feet of intestine were resected and continuity restored by an end-to-end anastomosis. There being no further evidence of injury, the abdomen was closed in layers without drainage.

The postoperative course was without morbidity. The only cause for concern was abdominal distention which was controlled by siphonage. The usual medication for the control of infection was resorted to, including blood transfusions, sulfonamides, and penicillin. The patient was discharged on Aug. 31, 1947, in good condition.

*Comment.*—The only controversial question in this case involves the choice of procedure in handling the injuries to the gravid uterus at operation. This problem was thoroughly discussed prior to operation. Would a cesarean hysterectomy rather than a classical section be the choice procedure? The weight of the evidence favored the classical section.

Reduction in the size of the uterus, in the quickest manner possible, in order to allow the surgeons ample time for exploration and repair, was the paramount reason for the decision made. Considering the possibilities of postoperative infection, it was realized that cesarean hysterectomy would give the patient a better prognosis. However, the necessity for rapid surgery overruled this argument. Under favorable circumstances, a cesarean hysterectomy is a more prolonged operation than a classical section.

The threat of infection was overcome by the administration of both the sulfonamides and penicillin.

### References

1. Belknap, R. W.: *J. Maine M. A.* 30: 13, 1939.
2. Belcher, C.: *Brit. M. J.* 1: 896, 1917.
3. Motta Maia and Vianna, G.: *Rev. de gynec. e d'obst.* 23: 319, 1929.



## PERFORATION OF THE UTERUS FOLLOWING A CRIMINAL ABORTION WITH PROTRUSION OF GANGRENOUS BOWEL INTO THE VAGINA\*

JOHN R. WOLFF, M.D., CHICAGO, ILL.

*(From the Henrotin Hospital, Chicago)*

At 11:00 P.M. on Sept. 26, 1947, a woman, her husband, and her alleged abortionist came into the emergency room of the Henrotin Hospital, under the following circumstances:

The patient had believed herself to be about three months pregnant. Her husband was elated, but she wanted an abortion. When the husband came home on the night mentioned, he found a message from his wife saying she had gone to a physician's office to have an abortion. The husband phoned the doctor at once, and told him not to do anything until he got there, that he was on the way. The husband rushed to the doctor's office. When he got there, the reception room was empty, but he noticed a light in the treatment room. He broke into this room. He found his wife lying asleep on the examining table. The doctor, with instruments in his hand, was sitting at the foot of the table and the floor was covered with blood. The husband threatened violence and forced the doctor to drive all three of them to the Henrotin Hospital. As soon as they arrived, the husband telephoned his personal physician, Dr. William Jack, who referred the problem to the author.

The patient was a 30-year-old white primigravida. She was sleeping lightly, but was easily aroused and well oriented. She admitted going to a doctor for an abortion. She recalled lying down on an examining table. She remembered the doctor giving her an injection in the vein of her left arm and telling her to count to twenty. The next thing she recollected was sitting in a car next to her husband.

She complained of nausea and lower abdominal pain. Her blood pressure was 110/72, temperature 98° F., pulse 88, respirations 22. Her skin was warm and moist. She seemed drowsy but not acutely ill. The cubital area of the left arm had a small recent puncture wound. The abdomen was not distended, but was soft and markedly tender below the umbilicus. An iodoform gauze pack was protruding from the vulva. This small vaginal pack (12 inches long) was removed and a sterile speculum inserted. Old blood and small clots were noted on the vaginal wall. The cervix had a recent bilateral laceration. A large amount of grayish blue tissue protruded from the cervix into the vagina.

The impression was that of an incomplete abortion. Due to the history of the interrupted operation, it was decided to transfer the patient to the operating room for examination under light anesthesia and removal of the tissue in the cervical canal.

Due to prolonged questioning by the police and states attorney's office, the operative procedure was delayed. The anesthetic was started at 2:25 A.M.—about four and one-half hours after the incident in the doctor's office. The patient's condition at this time was good, blood pressure 118/80, pulse 84, respirations 20, skin warm and moist. Pelvic examination at this time disclosed a uterus about the size of an eight to ten weeks' pregnancy. The small bilateral cervical lacerations were again noted. The tissue protruding from the external os was blue-gray in color, flat, and had the appearance of fetal membranes that had been torn and scraped. This tissue was grasped with a hemostat. Upon making gentle traction, large amounts of this tissue—about 24 inches long—fell into the vagina. It had a dark blue color and proved to be gangrenous small bowel, previously torn from the mesentery, with marks of previous trauma from grasping and scraping. A hemostat was placed on this tissue close to the cervix and the remainder amputated.

A laparotomy was performed at once through a median infraumbilical incision. A small amount of free blood and dark clots (about 150 to 200 c.c.) were in the lower abdomen. A large area of small bowel (estimated at six feet) was gangrenous, denuded from the

\*Presented before the Chicago Gynecological Society, Nov. 21, 1947.

mesentery, and had numerous "tracks" on its surface, as if scraped with a curette. This gangrenous bowel dipped through a hole into the uterus. The uterus was enlarged and ante-posed. The perforation was about 3 cm. in length and in the midline just above the level of the internal os.

The bowel was ileum and both the proximal and distal ends of normal attached bowel were located. The denuded and gangrenous bowel was removed, bleeding areas in the mesentery were ligated, the mesentery was approximated, and the bowel united by an end-to-end anastomosis. Although plasma and blood were given during the operation, the patient's pulse rate began to rise. It was then deemed best merely to evacuate the uterine contents, rather than do a hysterectomy. The perforated area was extended by incision into the fundus along the posterior wall of the uterus. The uterus contained placental tissue and denuded bowel. An assistant grasped the hemostat that had been left attached to the bowel in the vagina and removed that which had been in the uterus through the vagina. The placenta was peeled off manually. The uterus was sutured with three layers of continuous catgut. The abdominal wall was closed in the usual manner and without drainage.

The immediate postoperative condition was good. The patient was placed on a regime of intravenous nourishment with 500 c.c. of whole blood, 1,000 c.c. Amigen, and 1,000 c.c. 5 per cent glucose in saline daily. No oral food or liquid was allowed. 500 mg. streptomycin and 100,000 units penicillin were given intramuscularly every three hours.

The postoperative course was surprisingly smooth. Her highest temperature was 101.4° F., and she was afebrile after the fifth day. The pulse remained below 100 at all times. Bowel activity was good, with the passage of flatus and a soft stool within forty-eight hours.

On the third postoperative day, symptoms of a generalized peritonitis and ileus developed. The abdomen became markedly distended and profuse vomiting occurred. Peristaltic sounds were diminished, yet the patient was mentally bright and not at all toxic, temperature 101° F. and a pulse of 80. This rapidly responded to decompression therapy, (namely Wangenstein suction, rectal tube, and small enemas) within twenty-four hours. Numerous liquid defecations followed.

By the sixth postoperative day, the patient was taking food and liquids orally. Antibiotics and intravenous medication were stopped at this time. She was allowed to be out of bed on the eighth day, and went home on the twelfth postoperative day.

Follow-up examinations show her to be in excellent health. In January, 1948, she questioned her status regarding future pregnancies. Her menses were normal. Examination revealed normal pelvic structures. Gas insufflation showed nonpatency of the Fallopian tubes. This latter test was repeated at biweekly intervals through March with the same result. In April, 1948, this test showed patency of the tubes at 140 mm. Hg pressure. An x-ray with radiopaque material visualized normal pelvic organs and patent Fallopian tubes.

This case is reported, not only because of the dramatic and unusual factors involved, but because it demonstrates the following points:

1. Patients who have had a recent criminal abortion should be examined for evidences of possible uterine perforation and bowel injury.
2. Uterine perforation in itself may not lead to shock or internal hemorrhage.
3. When operation is indicated, suture of the perforated uterus may be preferred to hysterectomy.
4. The value of blood, intravenous protein therapy, and the antibiotics is well shown by the final result in this case.

30 N. MICHIGAN AVE.

## FETUS PAPYRACEOUS IN BINOVULAR TWIN PREGNANCY\*

D. J. SABATH, M.D., L. C. KVITEK, M.D., AND A. H. BAUGHER, M.D.,  
CHICAGO, ILL.

(From the Department of Obstetrics, Hospital of St. Anthony de Padua)

THE disclosure of a blighted partner, or of blighted partners, at the delivery of a viable fetus is rare and interesting. A scrutinizing review of the literature by Kindred<sup>1</sup> (1944) revealed only 180 such cases.

In 1937, Collins<sup>2</sup> stated that fetus papyraceous occurred particularly in twin pregnancies. Siegler,<sup>3</sup> in the same year, suggested that prenatal episodes of vaginal bleeding or of the development of toxemia were significant as warnings of the intrauterine death of one or more feti in multiple pregnancies. Ter Kuile and Parmalee<sup>4</sup> (1944) stressed the practical value of close attention to the history as well as to the physical findings of patients during the period of gestation.

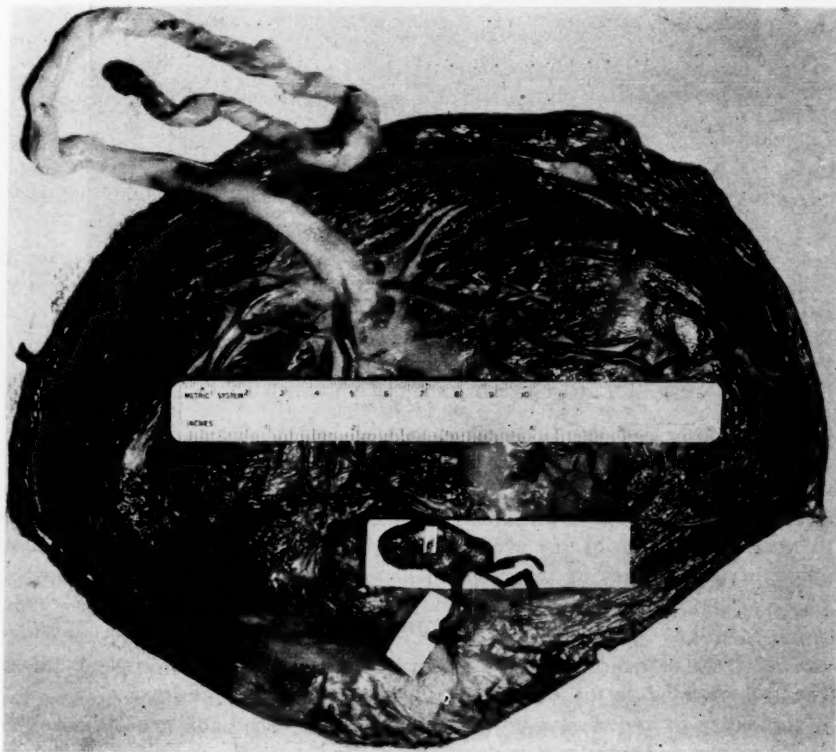


Fig. 1.—Fetus papyraceous attached to the fetal surface of the normal placenta.

Because of the relative infrequency of reports of fetus papyraceous in the literature, we present a report of a typical case in which a prenatal episode of vaginal hemorrhage prophesied the death of one of the fetuses of a binovular twin pregnancy.

Mrs. L. J., a 29-year-old, white female, gravida i, was first seen Oct. 22, 1946. The expected date of confinement was May 22, 1947. She related that there were numerous

\*Presented at a meeting of the Chicago Gynecological Society, May 16, 1947.

instances of multiple pregnancy in her family. The personal history and the physical and laboratory findings were negative. The prenatal course was uneventful except for an episode of vaginal hemorrhage Nov. 7, 1946. This bleeding subsided with only conservative management, and the patient went on to term, when she delivered spontaneously a living female infant on May 8, 1947, after labor of only eight hours and 40 minutes.

The placenta of this infant weighed 456 Gm. and it measured 21 by 12 by 3 cm. On the maternal surface there were three separate ischemic and partially fibrotic cotyledons. On the fetal surface there was a fetus papyraceous of 50 mm. crown to heel and 34 mm. crown to rump in length (Fig. 1). This fetus was attached by an umbilical cord 25 mm. in length to a slightly thickened fibrotic area three cm. removed from the margin of the normal placenta. The atrophied placental site adjacent to but separate from the larger placenta establishes this as a binovular twin pregnancy (Fig. 2).



Fig. 2.—X-ray demonstrating the fetus papyraceous and its placental site.

Measurements of the fetus papyraceous, differentiation of the limbs, development of the face, and the erect position of the head suggest the age of this fetus to be approximately 10 weeks. The time of the arrest of this blighted fetus may be directly correlated with the time of the incident of the prenatal hemorrhage.

### Summary

A case of fetus papyraceous is presented, in which the time of the fetal death may be chronologically correlated to an incident of prenatal vaginal hemorrhage.

The possibility of the disclosure of the intrauterine death of one or more fetuses of a multiple pregnancy as a result of such an episode indicates the need for careful interrogation for a history of ancestral multiple pregnancies; for alert evaluation of the first half of the period of gestation; and for the close scrutiny of the secundines.

### References

1. Kindred, J. E.: AM. J. OBST. & GYNEC. 48: 642, 1944.
2. Collins, R. M.: AM. J. OBST. & GYNEC. 33: 503, 1937.
3. Siegler, S. L.: AM. J. OBST. & GYNEC. 34: 1023, 1937.
4. Ter Kuile, R. C., and Parmalee, B. M.: AM. J. OBST. & GYNEC. 42: 345, 1941.

55 EAST WASHINGTON STREET



## HEMANGIOMA OF THE CERVIX

JOHN C. WEED, M.D., NEW ORLEANS, LA.

(From the Departments of Obstetrics and Gynecology, Tulane University School of Medicine and the Ochsner Clinic)

**A**MONG the pathologic lesions occurring in the human cervix there is a wide variety of benign and malignant processes. However, the standard textbooks fail to mention the existence of angiomatous lesions of the cervix. Both lymphangiomas and hemangiomas of the uterine fundus have been described, and hemangioma of the broad ligament has been noted. The only articles on hemangioma of the cervix found in a review of the world medical literature for the last ten years are those by Machado and Junqueira,<sup>1, 2</sup> who reported six cases. So far as we have been able to determine, no case of hemangioma of the cervix has been reported in the English literature. Such a case recently came under our observation.

### Report of Case

Mrs. R. F. P., white, aged 39 years, complained of numerous ailments, chiefly lower abdominal discomfort prior to the menses. This pain was suprapubic in location and varied in intensity. Occasionally, when severe, nausea and vomiting were also present. Backache was constant and bearing down pain was experienced with activity. Urinary stress incontinence was moderate. Dyspareunia, similar to the lower abdominal pain, was frequently noticed.

The menstrual cycles were regular at twenty-eight day intervals lasting five to six days with only a moderate flow. Dysmenorrhea was usually present. There was no intermenstrual bleeding. The patient had had but one pregnancy seven years previously, terminated after a long labor by forceps delivery. Periodic bleeding occurred throughout the entire pregnancy.

Physical examination revealed a normal female. Pelvic examination disclosed a lacerated perineum and a moderate cystocele. The cervix was hypertrophied and scarred from a previous laceration. The anterior and posterior lips were dark red, almost port wine, in color, softened, but not pulsating. The color faded to pale pink with light pressure. Neither ulceration nor eversion was noted, and the cervical canal was patent to a sound. The uterus was enlarged to about the size of a two months' pregnancy and contained several nodular eminences. With mild traction the cervix could be drawn to the introitus.

A diagnosis of cystocele, relaxed perineum, hemangioma of the cervix, multiple uterine fibroids, and prolapse of the uterus was made. On July 5, 1946, a vaginal hysterectomy and anterior and posterior colporrhaphy were performed. Convalescence was uneventful and the patient was discharged on the tenth postoperative day.

Gross examination of the surgical specimen revealed a uterus measuring 8 by 7 by 4 cm. One myoma measured 7 cm. in diameter. The remainder of the corpus was normal. The cervix was grayish white and pinkish red in the vaginal portion. A small area of superficial erosion surrounded the external os.

Microscopic examination of the cervix revealed numerous dilated capillary spaces throughout the vaginal portion, lined with a single endothelial layer, many engorged with red blood cells. The larger spaces were beneath the squamous epithelium. Deeper in the cervix these spaces were less numerous, but some cavernous sinuses could be identified in the region of the cervical glands. The connective tissue septa separating the sinuses varied considerably in thickness. Epidermidization of cervical glands, chronic cystic cervicitis, and endocervicitis were also noted. The leiomyoma was benign but did exhibit dilated vascular spaces not compatible with a diagnosis of hemangioma.

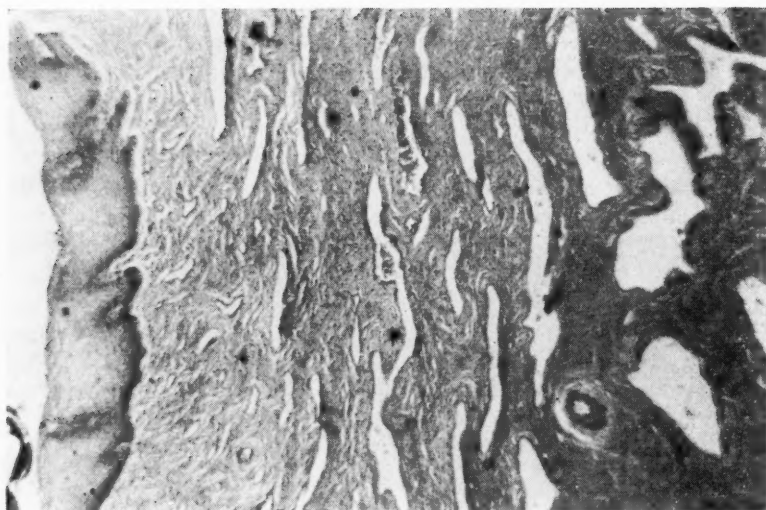


Fig. 1.—Photomicrograph ( $\times 80$ ) showing the portio vaginalis, with numerous dilated venous spaces occupying the superficial portion of the cervix.

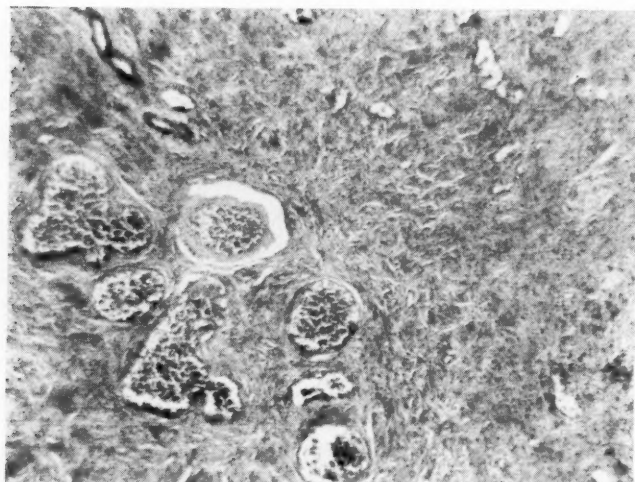


Fig. 2.—Deeper cervical tissue in the region of the cervical glands showing dilated venous spaces filled with erythrocytes.

### Comment

The six cases of hemangioma of the cervix reported by Machado and Junqueira were diagnosed by tissue section of surgical or biopsy specimens. Their patients complained of irregular vaginal bleeding, especially contact bleeding. Carcinoma of the cervix was suspected chiefly. The lesions described were wine colored, soft and spongy to the touch, fading on gentle pressure. Free bleeding occurred with biopsy, requiring sutures for control. Chronic cervical infection was noted in all sections and accounted for the induration upon which the suspicion of carcinoma was based. The presence of dilated venous spaces with an endothelial lining separated by septa established the diagnosis. These lesions were chiefly beneath the portio vaginalis. One patient on whom amputation of the cervix was performed subsequently was delivered of a viable fetus. No recurrence was noted at delivery, and there was no excessive loss of blood.

As in most of the cases described by Machado and Junqueira, our patient had a soft, wine colored cervical lesion, which faded on gentle pressure. Carcinoma was not suspected and a biopsy was not deemed advisable. Hysterectomy was performed because of the associated obstetric injuries and the uterine fibroid. A follow-up examination on Nov. 26, 1946, revealed no evidence of recurrence.

### Summary

A patient with hemangioma of the uterine cervix diagnosed clinically because of its gross appearance was subjected to vaginal hysterectomy for associated pathologic lesions. Microscopic examination of the cervix revealed a cavernous hemangioma involving chiefly the portio vaginalis.

### References

1. Machado, L. M., and Junqueira, M. A.: *An. Cong. brasil ginec. e obst.* 3: 245-247, 1942.
2. Machado, L. M., and Junqueira, M. A.: *Rev. de ginec. e d'obst.* 2: 20-24, 1941.

## SUDDEN MATERNAL DEATH FROM AMNIOTIC FLUID EMBOLISM\*

E. LLOYD WATKINS, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology of the Chestnut Hill Hospital)

TO THE date of this writing eleven authentic cases of fatal pulmonary embolism by amniotic fluid have been reported. Steiner and Lushbaugh<sup>1</sup> were the first to describe the condition in 1941 with a report of eight cases. The same authors added two more cases in 1942.<sup>2</sup> In February, 1947, Hemmings described the eleventh case.<sup>3</sup>

The purpose in reporting this case is to further emphasize the importance of embolic phenomena from amniotic fluid as an obstetric complication worthy of serious consideration. It is also of interest to note that this case illustrates the fact that in addition to the particulate components, the entrance of a large amount of amniotic fluid itself into the circulation can result in sudden death.

### Case Report

A 25-year-old white woman, gravida ii, para ii, was admitted to the Chestnut Hill Hospital at 1:00 A.M. on Jan. 6, 1947, with mild cramplike pains every five to eight minutes.

She was slightly past term, her estimated date of confinement being Jan. 2, 1947. She had had a twin pregnancy in 1944, the second child being delivered by a difficult version and breech extraction.

Labor proceeded indifferently until pains became regular by 7:00 A.M. on Jan. 6, 1947, and by 8:00 A.M. they were every two to four minutes, lasting fifty seconds. Membranes ruptured spontaneously at 8:00 A.M., and the cervix was six centimeters dilated and about one-half effaced. A single dose of Demerol (100 mg.) and scopolamine (gr.  $\frac{1}{150}$ ) was given at this time. Labor proceeded uneventfully until 9:50 A.M., at which time a rectal examination revealed a face presentation with almost complete dilatation of the cervix. The patient offered no unusual complaints, and pains persisted at two-minute intervals, lasting sixty seconds.

Preparations were being made to transfer the patient to the delivery room when she suddenly became cyanotic, took several convulsive gasps, and ceased to breathe. A faint radial pulse was discernible after respirations ceased. All restorative measures were of no avail. Death occurred about five minutes after the onset of symptoms.

There are two points of interest in the autopsy report as given by Dr. Thomas Cope of Chestnut Hill Hospital. These are: (1) the gross findings in the genitals, and (2) the microscopic picture of the lungs. A direct transcription of these follows:

*Genitals.*—The uterus was enlarged so that it almost completely filled the abdomen. It contained a full-term, male fetus of estimated weight 7 to 7½ pounds. The cervix had been effaced and completely or almost completely dilated. The baby's head was fully engaged in a face presentation so there was very considerable molding and a large degree of swelling of the chin and lower jaw. The baby was quite perfectly formed and appeared normal in every respect. It was attached by an umbilical cord of normal length to a normal placenta which was attached to the left side of the uterus. Little fluid remained within the uterus when it was opened. The muscle and decidual lining of the fundus appeared quite normal. The cervix was thinned out, dilated, and completely effaced. On the right side, 2 to 3 cm. above the cervical lip, there was a ragged tear 10 to 15 mm. across. A little blood and considerable free fluid exuded from this opening after the removal of the fetus. The opening led almost directly into the broad ligament which was enormously swollen and boggy with fluid. This swelling extended into the adjacent retroperitoneal space and up the kidney and reaching almost to the liver. All of these tissues were glistening and almost translucent with fluid. The total amount present appeared to be 500 c.c. or more.

\*Presented at a meeting of the Philadelphia Obstetrical Society on October 2, 1947.



*Lungs.*—The general structure was normal, although some of the air spaces appeared large and occasional loose ends of alveolar wall suggested rupture of the elements. On the other hand, there were many small areas in which the lung appeared compressed which appearance by the presence (generally throughout the tissues but especially in these areas) of numerous intra-alveolar macrophages laden with yellowish brown and black pigment granules. These resembled heart failure cells very closely but appropriate stains failed to demonstrate iron in the pigment. Vessels throughout were dilated with red cells, and in some areas there was leakage with intra-alveolar hemorrhages. In many of the capillaries and arterioles there were bits of foreign material of uncertain nature. These were accompanied by considerable infiltration of leucocytes, generally within the vessel but sometimes in its walls. This reaction was similar in appearance to that illustrated and described by Steiner et al., J. A. M. A. 117: 1245, 1941.

In correlating the pathologic findings with the rapid clinical course in this case the following points should be stressed:

1. The amount of particulate matter observed in the lungs was relatively small, and in itself was probably not sufficient to cause death.
2. The amount of fluid reaching the lungs must have been great. The patient literally "drowned" in her own amniotic fluid.
3. The process of extravasation of amniotic fluid into the right broad ligament and into the venous circulation by means of the small uterine tear must have been going on for some time before the onset of symptoms.
4. The possibility that some anaphylactic or anaphylactoid reaction could be an added factor in this case is also to be considered.

### References

1. Steiner, P. E., and Lushbaugh, C. C.: J. A. M. A. 117: 1245 and 1340, 1941.
2. Steiner, P. E., and Lushbaugh, C. C.: AM. J. OBST. & GYNEC. 43: 833, 1942.
3. Hemmings, Clarence T.: AM. J. OBST. & GYNEC. 53: 303, 1947.

The writer wishes to express his appreciation to Dr. Paul E. Steiner and Dr. Thomas A. Cope for their cooperation in the preparation of this report.

46 E. WILLOW GROVE AVENUE.

### Discussion

DR. J. ROBERT WILLSON.—It seems certain that fatal amniotic fluid emboli do occur, and the course of the embolism has been completely described by Dr. Watkins. On the other hand, I am not completely convinced that all the cases in the literature are deaths from amniotic fluid emboli. We know that chorionic epithelium is transported from the uterus to the lungs during pregnancy, and I do not believe anyone has proved as yet that the elements responsible for fatal emboli are not transported in the same manner in certain instances during labor. Careful examination of multiple sections of lungs of patients who die from other causes during or shortly after labor may demonstrate the same debris found in cases of fatal amniotic fluid emboli. In the original series of these cases reported, there were several who had very large blood losses that were not adequately replaced. I think it is not unlikely, since some of these patients survived for a considerable period of time, that the cause of death in this group was hemorrhage rather than amniotic fluid emboli. Amniotic fluid embolus is going to be a good out in the future for sudden deaths during delivery, and I think before making the diagnosis we should consider and eliminate all the other causes of sudden death which may occur during labor. The diagnosis should never be made, of course, without post-mortem confirmation of its existence and elimination of all other factors. In cases that are as thoroughly studied as Dr. Watkin's there can be no question of these other things, but we should all be very careful in assigning an obstetric death to amniotic fluid emboli unless we can be very sure there is no other reason which would leave us a little less blameless.

DR. WILLIAM R. NICHOLSON.—I have had two cases in past years that seem to me probably to fall into this category—one a multipara who had been perfectly normal during

pregnancy, blood pressure, urine, and circulation being within normal limits. She went into labor early in the morning; I was called, dressed, went to the telephone to call a taxicab when the telephone rang again and the nurse reported that she thought the woman was dead. When I reached the hospital I found that she was dead. I delivered a dead baby by forceps. She had not been bearing down, or rather she had just begun to bear down. No post-mortem was obtainable. The nurses stated that she had been perfectly normal up to the time they called me; that after that a nurse went back to see how she was and found her apparently dead. As a necropsy was not obtainable, the diagnosis is only provisional.

The other case was a multipara who had been in normal labor for a short time, probably a couple of hours, when I examined her and found a prolapse of the knuckle of the cord. She was immediately anesthetized and the easiest version that I ever did was performed. During this procedure she suddenly became blanched and, in spite of stimulation, she died about seven hours later. No postmortem was obtainable in this case.

Of course, as has been said above, these two cases are not proved, since there was no post-mortem examination in either case.

DR. WATKINS (Closing).—I think there are two important things we should keep in mind about this phenomenon. First is the time element. My personal feeling is that these patients die rapidly, and I am in complete agreement with Dr. Willson when he says those patients who have gone on for twenty-four to thirty-six hours probably have complicating factors involved along with the original process. Secondly, I do not believe we can make the diagnosis on any patient without accurate postmortem examination. We cannot say because we have a sudden, unexplainable death that the patient died from an amniotic fluid embolus unless the microscopic pulmonary pathology is clearly demonstrated.

## SARCOMA OF THE UTERUS\*

### Review of Cases at the Elizabeth Steel Magee Hospital

MORTIMER COHEN, M.D.,† AND CHARLES A. CRAVOTTA, M.D., PITTSBURGH, PA.

(From the Departments of Pathology and Gynecology, University of Pittsburgh, and the Elizabeth Steel Magee Hospital)

A REVIEW of the records at the Elizabeth Steel Magee Hospital for the twenty-five year period from November, 1920, to June, 1945, disclosed 16 cases of histologically proved sarcoma of the uterus in 23,859 gynecologic cases. In the same period there were 607 cases of carcinoma of the uterus, 173 occurring in the fundus, and 434 in the cervix. There were 2,017 fibroid tumors. The incidence of sarcoma was one in 38 malignancies of the uterus including body and cervix (2.6 per cent). and one to 126 fibroids (0.79 per cent).

The variations found in reported series of incidence of sarcoma in malignant disease of the uterus are as follows: Novak,<sup>1</sup> 4.5 per cent; Randall,<sup>2</sup> 8 per cent; Searight,<sup>3</sup> 2 per cent; Goldberger,<sup>4</sup> 3.5 per cent; Evans,<sup>5</sup> 2.5 per cent; Veit,<sup>6</sup> 2.6 per cent; Danforth,<sup>7</sup> 5.5 per cent; Curtis,<sup>8</sup> 2 per cent; Magee Hospital, 2.6 per cent. The highest was 8 per cent, the lowest 2 per cent.

### Clinical Data

The average age of the Magee series of patients was 46 years. The youngest was 26 and the oldest was 73 years. Six of the sixteen patients were more than 50 years old. Five had been delivered of children and one had aborted three times. Ten patients had never been pregnant. Six had undergone menopause. Four were spinsters. Fourteen were white and two were Negro.

Vaginal bleeding was the most common symptom, occurring in nine cases. Other symptoms varied. Loss of weight was present in only two, pain in the lower abdomen in six, profound weakness in only two. Dyspareunia and purulent discharge occurred once only.

Fibroid tumor of the uterus was present in ten patients, four of whom were unmarried. Metastases were found in five cases, three at operation and two at autopsy, with the lungs, liver, and kidneys being involved in one, and all of the organs of generation in the second.

X-ray examination of the chest and pelvis done in five patients failed to disclose any evidence of metastases.

Clinical diagnosis preoperatively included malignant tumor, ovarian cyst, degenerating fibroid tumors, submucous fibroid, and carcinoma of the fundus.

**Treatment.**—Panhysterectomy was done in five patients. Five had supravaginal hysterectomy, and three of these patients also received follow-up roentgen therapy. Three were treated solely with radium following diagnostic curettage, and one with roentgen therapy only. One received no operative treatment except biopsy of the cervix to confirm the diagnosis; exploratory laparotomy only was done in one patient. One patient was treated solely with roentgen therapy and transfusions of whole blood and plasma.

**Follow-up.**—Eleven patients are dead. Five are living and apparently well. In the five surviving patients the sarcoma was an accidental finding and was discovered as a result of gross and histologic study of the removed tissue. The intervals since operation for the living patients were one, three, eight, and fifteen years.

Eight patients, or 72 per cent, died in the first, one in the second, one in the fourth, and one in the fifth year after admission to the Hospital. All died of generalized sarcomatosis, but in one the supplemental diagnosis of influenza was made. This patient died

\*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Jan. 12, 1948.

†Died June 28, 1946.

at home four months after discharge from the Hospital, and probably also had generalized sarcomatosis, though no autopsy was secured.

*Diagnosis.*—The diagnosis of sarcoma was based on the classical criteria described in textbooks and articles on the subject. The clinical charts were studied and the necessary data were tabulated. In addition, all of the microscopic slides were assembled and reviewed so that the subject was considered as a whole. This was an important part of the survey and as a result two cases of highly cellular leiomyoma and two cases of mixed mesodermal tumor of the uterus were deleted from the series, leaving a total of sixteen cases. It is interesting that both deleted cases of cellular leiomyoma are still living some two years after operation, and both cases of mixed mesodermal tumor were dead about two years after the diagnosis was established.

### Classification

The tumors were classified into four groups.

*Group I.—Sarcoma originating in leiomyoma:* Of the sixteen tumors, less than one-half (7), were recognized as leiomyosarcomas. Histologically some of them were seen to be typically arranged in whorls, but others were found accidentally in what clinically were diagnosed as fibroids, singled out by the pathologist because of the unusual gross appearance. The yellow color of the tumor was of great importance, and the fleshy, soft consistency, often accompanied by necrosis and hemorrhage, was characteristic in the gross. The microscopic picture was the final criterion. While the tumor histologically resembles the fibrosarcoma, its outstanding differentiating feature is its tendency to grow in whorls with pleomorphic cells, often rich in tumor giant cell formation. Extensive necrosis of cells away from the vascular supply was common, and the "combing out" effect around the vessels, a point so diagnostic of sarcoma, was also characteristic. Atypical mitoses were a rather constant finding.

*Group II.—Sarcoma originating in endometrial stroma:* Three tumors originated in the endometrial stroma. The tumors were of the round cell type and, therefore, anaplastic. Two of the cases were associated with adenocarcinoma of the uterine fundus and were reported elsewhere.<sup>9</sup> Two of the three patients are dead, the third is living three years after operation. In this patient it is interesting and important to note that the sarcoma was an accidental finding in a uterus filled with leiomyomas. Round cell sarcoma originating in the stroma of the endometrium is difficult to understand. Since the endometrial stroma is said to be of connective tissue origin, the tumor originating from such a cell should be of fibroblastic origin, and, therefore, a fibrosarcoma. The characteristic cell in the tumor under discussion is a round cell and shows no fibroglia fibrils. As previously stated, it may be considered an anaplastic type of tumor.

*Group III.—Sarcoma originating in the cervix:* One case of sarcoma originated in the cervix. This, because of its grapelike growth, was considered to be sarcoma-botryoides in the adult. No striated muscle fibers nor other cellular abnormalities were found in this tumor. It recurred and finally proved fatal about a year after initial diagnosis. This grapelike sarcoma of the cervix is more rare in adults than it is in children, and represents the only primary sarcoma of the cervix seen at the Magee Hospital in twenty-five years.

*Group IV.—Miscellaneous:* The fourth group includes five cases. One rare type involved the uterine wall diffusely. It was an undifferentiated growth, a simple sarcoma of the uterine wall. The entire uterus was large and diffusely infiltrated with the growth. There were also small leiomyomas that were uninvolved. This patient lived about five years after the diagnosis was made. Following hysterectomy she seemed well for almost four years, and then developed a metastatic mass in the right upper quadrant. She was given x-ray therapy, and a resection of the colon was performed in an attempt to eliminate the metastases. Three months before her death she was again given 6200 r over six areas, but finally succumbed.

The second patient presented an anaplastic growth which began in a fibroid and later diffusely involved the uterus and cervix. Two cases were unclassified. One of these showed extensive metastases from sarcomatous growth taken at random from the uterus, and the other was one that showed an anaplastic sarcoma in what seemed grossly to be a fibroid.



Still another case was extraordinary. When first seen, the patient was in the third trimester of pregnancy. She had enormously enlarged breasts which proved to be involved in changes associated with sarcoma of the vulva, cervix, uterus, and ovaries. This was apparently a vivid example of the rapid stimulation of tumor growth during pregnancy. There were widespread metastases and death. During life the diagnosis was established by cervical biopsy. At autopsy it was not possible to identify the original site of the tumor, although it may have been the ovary. The growth was anaplastic and undifferentiated and, most remarkably, involved all of the organs of generation.

### Summary

1. A twenty-five year survey of the gynecologic service at the Elizabeth Steel Magee Hospital yields sixteen cases of sarcoma of the uterus, giving an incidence of 2.6 per cent of all malignancies of the uterus. The comparative incidence of sarcoma of all fibroid uterine tumors in this series was 0.8 per cent.

2. Only seven of the sixteen were histologically leiomyosarcomas, and ten of the sixteen originated in fibroids. Three originated in the stroma of the endometrium, and can be considered round cell sarcomas.

3. Five of the sixteen patients are still living, and longest survival period being fifteen years. It must be remembered that in all of the five surviving, sarcoma was an accidental finding in uteri removed for fibroids.

4. In one case of sarcoma complicating pregnancy the metastases were extensive and rapid.

### References

1. Novak, Emil: Textbook of Gynecology, ed. 2, Baltimore, 1944, Williams and Wilkins, p. 330.
2. Randall, Clyde L.: AM. J. OBST. & GYNEC. 45: 445-456, 1943.
3. Searight, Wilson: South. M. J. 34: 326-330, 1941.
4. Goldberger, Morris A.: J. Mt. Sinai Hosp. 7: 383-390, 1941.
5. Evans, N.: Surg., Gynec. & Obst. 30: 225, 1920.
6. Veit, John: Handbuch d. Gynakologie, 3 volumes, years 1897 to 1899. iii, i, p. 516.
7. Danforth, W. C.: Quart. Bull. Northwestern Univ. Med. School 16: 15-19, 1942.
8. Curtis, Arthur Hale: A Textbook of Gynecology, Philadelphia, 1942, W. B. Saunders Co., p. 338.
9. Cashman, Bender Z., and Cohen, Mortimer: Pennsylvania M. J. 45: 1183, 1942.

### Addendum

Since this paper was written one case of leiomyomasarcoma uteri has been found.

The patient was 53 years of age, white, married, who gave a history of menopause two years previous to admission. About three to four months later she developed post-menopausal vaginal bleeding and had several episodes since then. She lost 37 pounds in weight in the past six months. Lower abdominal pain has been present for the past ten years. She has had 15 children.

She was admitted on May 8, 1947, and was operated upon May 13, at which time a supravaginal hysterectomy, removal of cyst of mesentery, and lysis of adhesions between caecum and uterus were performed.

X-ray of chest on May 22, 1947, showed no evidence of parenchymal or bone metastases.

She had five doses of x-ray therapy beginning July 15 and discontinued on August 4 because of her clinical condition. She died on August 24, 1947, of generalized sarcomatosis, partial intestinal obstruction, and peritonitis.

No autopsy was performed.

## POSSIBLE HEMOLYTIC ANEMIA OF THE NEWBORN DUE TO HIGH TITER ANTI-"A" AGGLUTININ IN A GROUP "O" MOTHER

BERNARD A. G. WEISL, M.D., BROOKLYN, N. Y.

*(From the Department of Obstetrics and Gynecology, Methodist Hospital)*

MRS. L. S., aged 22 years, para 0, gravida i, a white woman of Italian extraction, first seen on Aug. 22, 1946, had her last menstrual period on Jan. 13, 1946, giving her an expected date of confinement of Oct. 20, 1946. Her past history was not remarkable, except for diphtheria in childhood, for which she received at least eight intramuscular injections of whole blood without any apparent ill-effect, and for which her father and his brother were the donors. Her antepartum course was not remarkable. The patient's blood type was "O," the Rh factor was positive, and her hemoglobin was 11.8 Gm. (Sahli). The father was typed recently and found to be type "O," Rh positive, of the subgroup Rh<sub>1</sub> and heterozygous, but his brother was dead.

On Oct. 13, 1946, after a labor of twenty hours and twenty-two minutes, she was delivered at 11:20 A.M. of a 6 pound 2 ounce baby boy, 17 $\frac{3}{4}$  inches long, from left sacroanterior position, frank breech, by breech extraction and the Wigand-Martin maneuver with the aid of a right mediolateral episiotomy. The baby cried spontaneously and appeared to be normal.

About six and one-half hours after delivery the baby was placed in an incubator and given oxygen because of its dusky color, but examination by a pediatrician revealed no abnormal findings other than slightly diminished breath sounds at the left lung base. On the following morning, October 14, the baby's hemoglobin was 16.1 Gm., the red blood count was 4.1 million, the white count was 23,000, polymorphonuclears 75 per cent, lymphocytes 21 per cent, monocytes 4 per cent, and 10 nucleated red blood cells were found. The blood type was "A" and the Rh was positive. The pediatrician who examined the child this day noted that the spleen was palpable and the baby was a little jaundiced. It appeared to be a thirty-eight weeks' gestation. He suggested the possibility of erythroblastosis fetalis and advised prophylactic transfusion. The baby was accordingly transfused on October 15 with 75 c.c. of type "A" Rh-positive whole bank blood, five days old. Prior to transfusion on October 15, the hemoglobin was 16.5 Gm. and the red blood count was 4.20 million, white count 25,000, with a normal differential and 10 nucleated red blood cells still present.

Two days following transfusion, on October 17, the hemoglobin was 21 Gm., the red blood count was 5.26 million. The next day, October 18, the hemoglobin had fallen to 16.5 Gm. with a red blood count of 4.1 million, white count 23,000, with no nucleated red blood cells. Six days following transfusion, October 21, the hemoglobin had fallen to 15.1 Gm., the red blood count to 3.5 million, and, because of this, the baby was given a transfusion on October 22 of 75 c.c. of type "A" Rh-negative whole bank blood, seven days old. Despite this transfusion and the clinical improvement of the baby, two days after the second transfusion, October 24, the hemoglobin was 14.9 Gm., the red blood count was 4.96 million. Six days following the second transfusion, October 28, the hemoglobin was 13.6 Gm. and the red blood count was 4.46 million, but the baby was in good condition and the jaundice, which had been present, had entirely cleared so that further transfusion was delayed. Since its condition continued to improve and it gained weight, going from 6 pounds to 6 pounds 4 ounces on October 31, its eighteenth day, no further transfusion was given. On the twenty-second day after birth, November 4, the hemoglobin had risen to 15 Gm. with a red blood count of 5.01 million. The baby was discharged home in good condition on its twenty-fourth day, November 6, weighing 6 pounds 9 $\frac{1}{2}$  ounces, 7 ounces above birth weight.

On the basis of red blood counts, this baby showed no real anemia, the counts being above four million, with one exception when it was 3.5 million (Table I). However, the hemoglobin determinations (Sahli method) may indicate a slight anemia, since they fell from

an initial 16.1 Gm. to a low of 13.6 Gm. during the first fifteen days post partum, despite two whole blood transfusions. The temporary nature of the rise in hemoglobin following the first transfusion and the lack of response to the second, plus the failure to maintain a hemoglobin level, give rise to the suspicion that some process in the baby was destroying red blood cells.

TABLE I

DATE 1946	AGE IN DAYS	HEMO- GLOBIN GRAMS (SAHLI)	RED BLOOD CELLS (MIL- LIONS)	LEU- COCYTES	POLYS	LYMPHS	MONO	EOSIN	NUCLE- ATED R.B.C.
Oct. 14	1	16.1	4.10	23,000	75	21	4	0	10
Oct. 15	2	16.5	4.20	25,000	56	40	2	2	10
Oct. 15	2	Transfusion 75 c.c. Type "A" Rh Positive Whole Bank Blood, Five Days Old							
Oct. 17	4	21.0	5.26	---					
Oct. 18	5	16.5	4.10	23,000	68	27	4	1	None
Oct. 21	8	15.1	3.50	---					
Oct. 22	9	Transfusion 75 c.c. Type "A" Rh Negative Whole Bank Blood, Seven Days Old							
Oct. 24	11	14.9	4.96	---					
Oct. 28	15	13.6	4.46	---					
Nov. 4	22	15.0	5.01	---					
Nov. 6	24	Discharged Home							

Because of the possibility of a mistake in the determination of blood types, blood specimens of the father, mother, and baby were sent to a research laboratory where the following findings were reported, which were in agreement with the original typings that were done:

"Mother: Group "O," Rh Positive of the Subtype Rh<sub>2</sub>, and heterozygous.

Father: Group "A," Rh Positive of the Subtype Rh<sub>1</sub>, and heterozygous.

Baby: Group "A," Rh Positive of the Subtype Rh<sub>1</sub>, and heterozygous."

In 1936 Jonsson<sup>1</sup> reported that a mother of blood Group "O" may develop a higher titer of anti-"A" agglutinin if she is carrying a fetus with the "A" agglutigen than if the fetus were Group "B" or Group "O." C. A. Smith<sup>2</sup> notes that "Such a development would of course render her a most unsuitable donor for transfusion of blood to her infant, and thus offers one more reason for careful crossmatching of bloods in transfusion to the newly born patient." Because of Jonsson's findings, specimens of the mother's blood were sent to a research laboratory, starting October 28, the fifteenth postpartum day when the anti-"A" agglutinin level had an end point in saline at a dilution of 1:1,000 and in albumin about 1:2,000. On the fortieth postpartum day, Nov. 22, 1946, the end point of the anti-"A" titer was 82 million in saline and albumin.

Further specimens were sent to this research laboratory, and on Jan. 22, 1947, the report states: "Exhaustive tests were performed on the serum in an effort to demonstrate that the mother had an immune type of anti-A agglutinin, which might have been stimulated by a Group A baby. We were unsuccessful in proving this, although once more we find a relatively high titer of anti-A agglutinin, which may or may not be significant in presupposing that the baby had mild anemia due to the action of anti-A on its A cells." It was suggested that another test be done on the mother's blood in about a year to determine the level of the anti-"A" titer.

Accordingly, on Nov. 17, 1947, thirteen months post partum, a specimen of the mother's blood was again tested and the anti-"A" titer was found to have an end point of 4,000 in saline and albumin as compared with 82 million on Nov. 22, 1946. Because of this it is felt that this was possibly a case of mild hemolytic anemia of the newborn due to specific stimulation by the "A" baby on the "O" mother.

Reviewing the blood work of this case, Diamond<sup>3</sup> states, "As regards the average anti-"A" titer of nonpregnant women and of men, it usually varies between a dilution of 16 and about 500 at a maximum. However, gravid women, particularly of Group "O" or Group "B," who are pregnant with "A" children, often show a rise which is probably not important clinically. The maximum figures we have found in such patients have seldom exceeded 5,000. We have a few instances of a titer as high as 100,000 without clinical disease in the baby. Certainly the figure of several million is a most unusual one and is quite consistent, or, in fact, even convincing evidence of the mild hemolytic anemia which the child had."

This anti-"A" titer of 82 million is the highest that I have been able to find in the literature.<sup>4</sup> In a later communication, Diamond stresses the point, "that the level of agglutinin is no index as to how much harm the baby will sustain whether it is anti-Rh, or anti-"A," or anti-"B."

Fifteen months after birth this baby is alive and well and has progressed normally and has no apparent sequelae from its mild hemolytic anemia.

This case is being reported to record a possible case of mild hemolytic anemia of the newborn caused by a high titer anti-"A" agglutinin in a Group "O" mother with a Group "A" baby.

All the special blood work in this case was done by the Blood Grouping Laboratory of Boston, Massachusetts, and received the special attention of Louis K. Diamond, M.D., who devoted much time and care to the analysis of this case, and to whom special thanks are given.

W. F. Watton, M.D., the pediatrician in the case, is thanked for his cooperation and for the excellent care of the child.

### References

1. Jonsson, B.: *Acta Path. et Microbiol. Scand.* 13: 424, 1936.
2. Smith, C. A.: *The Physiology of the Newborn Infant*, p. 289, Springfield, Ill., 1945, Chas. C. Thomas.
3. Diamond, Louis K.: Personal communication.
4. Potter, E.: Rh, p. 139, Chicago, 1947, Year Book Publishers.



## ACUTE SUPPURATIVE APPENDICITIS AND PREGNANCY AT TERM

SAMUEL J. TURNER, M.D., AND MANUEL B. WEISS, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics of the Mount Sinai Hospital and the Chicago Medical School)*

**A**CUTE appendicitis is a relatively uncommon and very serious complication when occurring during pregnancy at term. The incidence based on case reports as presented by Baer, Reis, and Arens,<sup>1</sup> Cosgrove,<sup>2</sup> Norton and Connell,<sup>4</sup> Meiling,<sup>3</sup> and Priest<sup>6</sup> varies from one to three for every ten thousand births.

All authorities agree that immediate surgical intervention is the treatment of choice and may be a lifesaving measure for the mother as well as for the infant. However, the surgical procedures advised meet with considerable controversy. Baer, Reis, and Arens,<sup>1</sup> Cosgrove,<sup>2</sup> Norton and Connell,<sup>4</sup> Te Linde,<sup>7</sup> Titus,<sup>8</sup> Priest,<sup>6</sup> and Stander<sup>9</sup> advise immediate appendectomy with great caution so as not to interfere with the pregnancy at the time of operation. The end results obtained by these authors justify their conclusions. During the past two years, others have been advocating a much more radical approach. E. M. C. Passos,<sup>5</sup> quoted by Greenhill, prefers an appendectomy and a simultaneous delivery of the baby through the lower passages in multiparous women where the cervix can be dilated by *accouchement forcé*. In primiparas, he advises cesarean section prior to appendectomy. Meiling<sup>3</sup> urges termination of pregnancy by transverse laparotrachelotomy followed by appendectomy in all cases of acute appendicitis during the last two months of gestation. Post-operatively, he advises the use of massive doses of sulfonamides and antibiotics.

It is because of the existing disagreement in the management of this serious complication of pregnancy that the following case is considered worth reporting.

### Case Report

M. M. (History No. 155720), 22-year-old married, white woman, para 0, gravida i, was admitted to the hospital at 8:20 A.M. on Nov. 16, 1946, two weeks before the expected date of confinement. The patient stated that, after an uneventful night, she awoke voluntarily at 5:30 A.M. to prepare breakfast. About 6:00 A.M., after urinating without any pain or discomfort, she suddenly experienced a severe, stabbing pain in the right lower quadrant of her abdomen. This colicky pain recurred at intervals of three to five minutes, and partial relief was obtained by lying on her back and keeping her right thigh flexed upon her abdomen. She was slightly nauseated, but did not vomit.

The prenatal history revealed a last menstrual period on Feb. 24, 1946. Her family history was negative. She had a noncomplicated mitral regurgitation which gave her no cardiac difficulties. The blood pressure remained normal at 120/70 and the total weight gain was 23 pounds. She had an acute upper respiratory infection during the third month and an acute right pyelitis during the eighth month of gestation. Pelvimetry revealed a medium-sized gynecoid type of pelvis. A complete blood count was within normal limits, the Kahn reaction was negative, the Rh factor was positive, and urinalysis was normal at all times, except that it was loaded with pus cells for several days during the time she had pyelitis.

Examination upon admission to the hospital disclosed a well-nourished, 22-year-old, white woman, lying on her back keeping her right thigh somewhat flexed upon her abdomen, with a general appearance of being uncomfortable but not acutely ill. Temperature was 99.2° F., pulse 90 and blood pressure 120/80. The eyes, ears, nose, and throat were negative. The breasts and lungs were normal. The heart had a loud systolic murmur at the apex which was transmitted to the axilla. The abdomen appeared to be the size of a full-term pregnancy. The height of the fundus was 38 centimeters, the position of the baby right occipitotransverse and the fetal heart sounds were of good quality. Uterine contractions were not present. There

was exquisite tenderness in the right lower quadrant at the level of the umbilicus and none over the region of the kidneys. Rectally, the presenting part was at zero to minus one station and the cervix was well effaced but not dilated. A catheterized urine specimen was negative. A complete blood count revealed 3,420,000 red blood cells, 12,600 white blood cells, 73.2 per cent hemoglobin, 6 stabs, 84 segments, 9 small lymphocytes and one monocyte.

The preoperative diagnosis was twisted ovarian neoplasm, or acute appendicitis complicating pregnancy at term. A laparotomy was performed through a high gridiron incision, five hours after the onset of symptoms. About 100 to 150 c.c. of turbid fluid were aspirated from the peritoneal cavity. The appendix appeared indurated, was covered with a thick purulent exudate, and was fixed behind the cecum at the level of the right posterior iliac crest. An appendectomy was done and the abdomen closed in layers without drainage.

The pathologic diagnosis, as reported by the pathologist, was acute suppurative appendicitis and periappendicitis.

The immediate postoperative condition was satisfactory. An initial dose of 100,000 units of penicillin was followed with 40,000 units intramuscularly every three hours. Other supportive measures included intravenous fluids, sedation and Wangenstein suction.

At 6:30 P.M. on Nov. 17, 1946, thirty hours after surgery, the membranes ruptured spontaneously. Uterine contractions at five-minute intervals began two hours later. Rectal examination at the time revealed no cervical dilatation and station of minus one to zero. 1,000 c.c. of 5 per cent glucose in saline intravenously, two doses of 100 mg. of Demerol and  $\frac{1}{150}$  grain of scopolamine each, plus oxygen inhalation were administered during the next twelve hours. The cervix was completely dilated and the presenting part came down to a plus one station at about 7:00 A.M. on Nov. 18, 1946. At 8:00 A.M., after one hour in the second stage, the presenting part came down to a plus two station. The condition of the patient and the fetus appeared satisfactory. Under nitrous oxide-oxygen anesthesia, a deep mesiolateral episiotomy was followed by rotation of the occiput from a right occipitoposterior to a right occipitoanterior position with Kielland forceps. A Simpson forceps was then applied and a 7 pound, 15 ounce, living, male infant was delivered. The placenta soon followed and the episiotomy was repaired.

The patient did generally well except for a temperature rise to 101.6° F., four hours after appendectomy and another rise to 102° F., twenty-four hours after delivery. 500 c.c. of whole blood were given on the fourth postpartum day to overcome a moderate anemia. She was discharged from the hospital five days after delivery. She could have remained in the hospital a few more days but the obstetric floor had to be cleared because one of the mothers had developed chicken pox. She refused transfer to another floor and insisted on going home. Re-examination one week and five weeks later revealed that the patient and baby were enjoying excellent health.

### Comment

The case presented adds further proof that prompt operative intervention is most imperative in suspected appendicitis complicating pregnancy near term. The classic symptoms of acute appendicitis as given in most surgical textbooks were not present in this case. The onset was with pain in the right lower abdomen and mild nausea. No other symptoms developed. Yet, acute suppurative appendicitis with considerable peritoneal response was found within five hours after the onset. There is no doubt that further procrastination might have been hazardous for the patient as well as for her baby.

The end result in our case speaks favorably for the method of prompt appendectomy and allowing the pregnancy to take its natural course.

### Summary

1. The patient whose case is presented had an acute suppurative appendicitis and periappendicitis complicating pregnancy at term.
2. Appendectomy was performed five hours after the onset of symptoms.
3. The fetal membranes ruptured spontaneously and labor began thirty hours after surgery.

4. Delivery of a living, seven pound, fifteen ounce, male infant was accomplished through the lower passages forty-four hours after appendectomy.

5. Mother and baby left the hospital in good condition five days after delivery.

### References

1. Baer, J. L., Reis, R. A., and Arens, R. A.: J. A. M. A. 98: 1359, 1932.
2. Cosgrove, S. A.: AM. J. OBST. & GYNEC. 34: 469, 1937.
3. Meiling, R. L.: Surg., Gynec. & Obst. 85: 512, 1947.
4. Norton, James F., and Connell, John M.: Am. J. Surg. 32: 325, 1936.
5. Passos, E. M. C.: Yr. Book Obst. & Gynec., 1946, page 79. Quoted by Greenhill.
6. Priest, F. O.: AM. J. OBST. & GYNEC. 31: 878, 1936.
7. Te Linde, R. W.: Operative Gynecology, Philadelphia, 1945, J. B. Lippincott Co.
8. Titus, Paul: Management of Obstetric Difficulties, Saint Louis, 1946, C. V. Mosby Co.
9. Stander, H. J.: Textbook of Obstetrics, New York, 1946, D. Appleton-Century Co.

30 NORTH MICHIGAN AVENUE.

## Department of Reviews and Abstracts

---

### Selected Abstracts

---

#### Abortion

**Canna, S.: Prematurity and Abortion During War Time, *La Ginecologia* 13: 515, 1947.**

Stillbirths, incidence of prematurity, and abortions in a consecutive series of 6,000 deliveries are reported by Canna, including pre- and war-time cases.

During the period covering the years 1933-1939 (prewar period), cases of abortion accounted for 12 per cent of the total number of observed pregnancies, whereas, during the period covering the years 1942-1945, the abortion rate rose to 15 per cent. This increase affected primiparas and multiparas. In primiparas the rate increased from 4 per cent to 7 per cent; in multiparas from 6 per cent to 20 per cent. Agricultural laborers showed the highest increase.

Prematurity and stillbirths also showed an increase during the war of from 13.8 to 21.8 per cent of the total number of pregnancies. Increase was highest in factory workers.

Canna attributes the increase in abortions mainly to the very definite increase in syphilitic infections observed during this period and the increase in prematurity to the heavy factory work to which the women were not accustomed.

GEMMA BARZILAI.

#### Analgesia

**Rogers, Walter C.: Spinal Anesthesia in More Than Five Thousand Vaginal Deliveries, *West. J. Surg.* 236: April, 1948.**

The widely accepted thesis that spinal anesthesia is dangerous in obstetrics is strongly denied. The procedure was used in 5,067 deliveries. Advantages over general anesthesia are: mothers awake and cooperative, relaxation of cervix and perineum, patient quiet during episiotomy repair, more rapid postpartum recovery, and low incidence of narcotized babies. A few serious anesthetic reactions are reported in this series but these occurred early in the experience before the author had learned to keep the dose low. Headaches following spinal anesthesia continue to be an annoying side effect, occurring in about 10 per cent of the cases. There were no maternal deaths and no fetal deaths attributable to the anesthesia.

Administration of the anesthetic agent in a hyperbaric solution is strongly recommended, the preferred drug being Pontocaine in a dose of 3 mg. to 10 mg. in a 2 per cent glucose solution.

WILLIAM BICKERS.

#### Cesarean Section

**Adama, Theodore W.: A Statistical Review of Two Hundred and Forty-One Consecutive Cesarean Sections, *West. J. Surg.* April, 1948, p. 243.**

A cesarean incidence of 7.9 per cent in a series of 3,045 deliveries managed in private practice is reported by the author and justification for the high incidence is presented. In



the total series of patients, the method of delivery was: spontaneous delivery 18.3 per cent, low forceps 61.2 per cent, midforceps 3.8 per cent, breech extractions 3.4 per cent, versions and extractions 0.3 per cent, craniotomy 0.03 per cent, and cesarean section 7.9 per cent.

The laparotrachelotomy was a favored operation, the classical operation being employed only in specific indication. Cesarean hysterectomy was used 22 times, 4 for Couvelaire uterus, 2 in uterine atony, and 2 in uterine infection. The remaining Cesarean hysterectomies were done because of large fibroids.

The high incidence of cesarean section here reported is justified on the basis that, while a single specific indication for the operation is not always present, there was in every case one or more obstetric or medical complications, the sum of which was sufficient to justify the procedure. In 34.4 per cent of the sections, the indication was previous cesarean section. Placenta previa in which bleeding was above minimal was considered adequate indication: those showing evidence of prenatal separation of the placenta were likewise submitted to section unless the cervix was partially dilated by the patient already in labor. There were seven women with definite heart disease in the cesarean group, and no maternal or fetal death, which makes one surmise that the heart disease was not of the severe type. The toxemias did not provide an indication. There were no maternal deaths, an incurred mortality of 0.8 per cent, and a morbidity rate of 49 per cent. It is believed that the final judgment upon the obstetric ability of an operator should be based upon maternal and fetal mortality, with less attention paid to his cesarean incidence.

WILLIAM BICKERS.

### Endocrinology

**Rakoff, A. E.: The Endocrine Factors in Pelvic Tumors With a Discussion of the Papanicolaou Smear Method for Diagnosis, Radiology 50: 190, 1948.**

The author reviews the literature concerning the various clinical findings relative to ovarian dysfunction and cancer of the uterus. He also reviews the experimental work on the carcinogenic effect of estrogens.

In his study of the vaginal smear method of diagnosis of cancer, Rakoff believes that the procedure is sufficiently worth while to be made a routine part of the examination. He also states that a goodly percentage of cancers can be missed from a single examination. Endometrial cancers are harder to detect by the smear method than cervical cancers. The author feels that the best procedure is to take smears from both the cervix and the vagina for the most accurate diagnosis.

WILLIAM BERMAN.

**Marrian, G. F.: The Corpus Luteum Hormone, Edinburgh M. J. 54: 611-619, 1947.**

Progesterone is produced by the corpus luteum, or by the placenta after the twelfth week of pregnancy. Metabolic conversion occurs mainly, but not exclusively, in the endometrium. The chief urinary metabolite is sodium pregnanediol glucuronate, the amount of which can be estimated by weighing the purified salt, or by a more sensitive colorimetric determination of pregnanediol freed by hydrolysis. Since pregnanediol is also a metabolite of desoxycorticosterone and possibly other steroids, and, since it is not the only metabolite of progesterone, we cannot assume a quantitative relationship between endogenous progesterone production and pregnanediol excretion.

Urinary pregnanediol appears 24 to 48 hours after ovulation, and rises to a maximum level of 2 to 8 mg. per day in the late cycle. In early pregnancy, excretion averages 10 mg. per day, but soon after the tenth week the value begins its climb to about 75 mg. per day, with an abrupt fall at parturition. Stilbestrol administration increases pregnanediol excretion during pregnancy, and may be of value in preventing abortion, premature labor, and toxemias of pregnancy.

Pregnanediol determinations may be used to diagnose anovulatory menstrual cycles, and as a rapid pregnancy test.

IRVING L. FRANK.

**Bourne, Aleck:** *Endocrines in Gynaecology*, Brit. M. J. 4489: 79, 1947.

Bourne reviews the progress in this field of medicine since its initiation by Stockard and Papanicolaou in 1917. The present-day concept of the physiology of the various hormones is first discussed. He postulates the existence of receptor substances in the vaginal mucosa, endometrium, and other tissues in the genital tract which are able to react with the estrogenic molecule and, by chemical or other union, perform a specific function. The absence of such substance in other tissues of the body is obvious. The author stresses the fallacious conclusions with reference to human physiology that are often drawn from animal experimentation.

In approaching the problem of therapeutics, he stresses the lack of exact knowledge as to whether we are dealing with a deficiency, excess, or disordered rhythm in the production of the hormones concerned. In the evaluation of therapeutic response he suggests dividing the sex-organ disabilities into those which are functional and those which are objective or organic. In the latter group, the only one in which we can be certain of success is in suppression of lactation. The results of treatment in pelvic hypoplasia with amenorrhea and sterility, atrophy of vulvovagina, leucoplakia, and metropathia have been disappointing. Likewise the treatment of functional disorders such as dysmenorrhea and repeated abortion gives disappointing results.

In summary, the disappointments in therapy are attributed to plunging too quickly from the endocrinology of animals to its application in clinical medicine. Another difficulty is the complexity of biochemical assay in various organic fluids from qualitative and quantitative points of view and their impractical aspects in practice.

R. G. DOUGLAS.

### Endometriosis

**McGuff, Paul, Dockerty, Malcolm B., Waugh, John M., and Randall, Lawrence M.:** *Endometriosis as a Cause of Intestinal Obstruction*, Surg., Gynec. & Obst. March, 1948.

The paper presents an analytical study of sixteen cases of intestinal obstruction caused by endometriosis. The usual symptoms of lower intestinal obstruction, associated with acquired dysmenorrhea, sterility, and pelvic pain should bring the possibility of this condition to mind. The treatment is relief of the obstruction, usually by resection. The question of removal of the pelvic organs will depend on the extent of the endometrial implants. If there is hope of future pregnancy, bilateral oophorectomy should be avoided. A plea is made for the more frequent use of frozen sections to prevent confusing this lesion with carcinoma.

LOUIS M. HELLMAN.

### Gynecology

**Frank, Robert T.:** *Dyspareunia: A Problem for the General Practitioner*, J. A. M. A. 136: 361, 1948.

The author reviews his clinical experiences over a period of years in the treatment of dyspareunia. These cases represented 1.5 per cent of his gynecologic practice over the same number of years. Dyspareunia that developed with marriage was primary and when the onset occurred later it was termed secondary and treated accordingly. It was interesting to note that of the 349 patients reviewed, normal pelves were noted in 63 patients. Fifty-five per cent of these women showed neuroses and psychoneuroses, in sharp contrast to the percentage of the total figure (349) which was only 25 per cent. The husband problem predominated in 36 cases. In primary and secondary dyspareunia, local therapy combined with enlightenment and orientation proved effective.

WILLIAM BERMAN.

**Norment, W. B.:** *A Method of Study of the Uterine Canal*, South. Surgeon, Dec., 1947.

Direct visualization of the uterine cavity and x-ray hystrogram are advocated for the study of gynecologic patients. For hystrogram study, and organic iodine in alcohol by Rayopake is recommended in preference to oil. Direct visualization of the uterine cavity is obtained by the insertion of a translucent and transparent bag over a plastic cannula which is inserted into the uterine cavity.

The author now uses a transparent plastic sheet with a cannula attached to the optic instrument for obtaining photographs of the uterine cavity. He reports a satisfactory visualization of intrauterine pathology with this instrument.

WILLIAM BICKERS.

**Charles, A. H.: A Case of Hydatidiform Mole at Age 52, Brit. M. J. 4473: 460, 1946.**

The case is reported because of the advanced age of the patient. In a review of the literature, twenty pregnancies in women of 50 years of age were found, five of whom had moles. The condition is encountered two and one-half times more frequently in women over 40 years of age. Most authors favor hysterectomy in this age group because of the incidence of chorionepithelioma following the condition. The case report concerns a 52-year-old woman who had vaginal spotting for 2 months. A dilatation and curettage was done and the pathological examination of the tissue interpreted as carcinoma. A second curettage in another institution revealed the true nature of the condition. A complete hysterectomy and bilateral salpingo-oophorectomy were done. The suspected pathology was confirmed and the subsequent course was uneventful.

R. G. DOUGLAS.

### Gynecologic Operations

**Smith, George Van S., and Mulligan, William J.: Dicumarol Prophylaxis Against Venous Thrombosis in Women Undergoing Surgery, Surg., Gynec. & Obst., April, 1948.**

This paper is a progress report on the administration of Dicumarol prophylactically to 2,353 operative patients at the Free Hospital for Women. The objective of this therapy was the reduction of the incidence of postoperative embolic phenomena. This seems to have been accomplished, for the incidence of thrombic complications in the four-year period prior to therapy was 1:90, while, in a similar period during which the patients were treated with various dosage schedules of Dicumarol, the incidence fell to 1:138. The authors point out the necessity of following the patients with prothrombin levels in order to secure adequate therapeutic results.

LOUIS M. HELLMAN.

**Reiner, Walter C.: Gigantic Ovarian Cyst Developing in a Thecoma, West. J. Surg., April, 1948, p. 205.**

Large ovarian tumors have become a rarity in civilized countries. The author reports a case of thecoma with cystic changes. The patient, aged 62, was admitted to the hospital because of a large abdominal mass, edema of the ankles, dizziness, and a bloody vaginal discharge of four years' duration. She was emaciated, the hemoglobin was 47 per cent, the urine contained a trace of albumin and a moderate number of red blood cells. She was given frequent small feedings of nourishing food, supplemented with cevitamic acids and vitamin K and liver extract. At the initial operation, an incision was made into the cyst and a tube inserted. Six thousand cubic centimeters of dark brown fluid were drained slowly. She was then returned to her room where the tumor was slowly depressed over a period of three days. At the end of this time, the tumor was removed with great difficulty, because of many adhesions to all of the abdominal organs.

Pathologic examination revealed a solid tumor having the appearance of a thecoma surrounded by huge areas of cystic degeneration. The patient made an uneventful recovery. The total amount of fluid removed was 26,500 c.c., the weight 60.1 lb.

WILLIAM BICKERS.

**Dunphy, J. Englebert: A Combined Perineal and Abdominal Operation for the Repair of Rectal Prolapse, Surg., Gynec. & Obst., April, 1948.**

An operation for complete rectal prolapse is described. This is not an original procedure but a combination of various techniques described by others and involves: 1, circular amputation of the prolapsed segment of rectum; 2, excision of the redundant hernial sac; 3, suture of the levators anterior to the rectum, all from below. The following are then per-

formed transperitoneally: 1, mobilization of the rectum and suture of the transversalis fascia; 2, closure of the pouch of Douglas; 3, fixation of the pelvic colon to the lateral wall of the pelvis. The operation has been successfully performed on four patients. LOUIS M. HELLMAN.

**Shaw, Henry N.: Prolapse of the Vaginal Vault Following Hysterectomy: A New Method of Repair, West. J. Surg. 56: 127, 1948.**

Prolapse of the vaginal vault following total hysterectomy is the result of poor surgical technique. Failure to suture the broad ligament, uterosacral and uterovesical ligaments into the vault will often be followed by this unfortunate sequel.

Various methods have been described for replacing the prolapsed vagina: suture to the presacral fascia, the use of fascia lata loops, abdominal fixation, and the LeFort operation. There are reported successful operations upon three patients with vaginal prolapse by the use of fascia strips from the anterior rectus sheath. These strips were brought down extra-peritoneally and sutured to the vaginal vault, thus maintaining the vagina in its normal anatomical relation.

WILLIAM BICKERS.

### Mammary Glands

**Davison, T. C., and Letton, A. H.: Testosterone in Far Advanced Breast Cancer, South. Surgeon 14: 170, 1948.**

Ulrich first reported the treatment of breast cancer with androgen. Adair and Herman have contributed to the study by further publications. Androgens apparently delay or retard the cellular activity particularly of the metastatic neoplastic cell. Recalcification of bone in the site of metastases has been observed and biopsy of metastatic region following treatment with 50 mg. of testosterone daily reveals some fibrosis about the neoplastic cells with apparent inhibition of nuclei activity in the malignant cells.

Eight patients are reported. The first had a mastectomy for cancer followed by x-ray therapy and subsequently developed metastases of the ilium. Calcification of the ilium occurred following testosterone therapy. The second case had a somewhat similar history and the vaginal smear showed evidence of estrogenic activity. Following testosterone therapy there was partial recalcification of the right ilium and she gained weight. The third patient had metastases to the rib and lung and her vaginal smear showed marked estrogenic activity. Large doses of testosterone failed to change the picture in this case.

Case 4 was similar, but there was marked regression of rib metastases following testosterone and the patient returned to full improvement and was comfortable for a long period. The other four cases showed similar response to treatment.

Seven of eight patients had some pain relief and gained weight on testosterone therapy. Four patients with extensive metastases were able to return to work. One patient who had tissue metastases only had an excellent result for over fifteen months. The best results are found in patients who show evidence of estrogenic depression. Poorer results are shown in those who show persistent estrogenic activity. Masculinizing effects are noted, to which patients do not object, since they realize the gravity of their condition and are grateful for the relief of pain.

WILLIAM BICKERS.

**J. B. Enticknap: Angioblastoma of the Breast Complicating Pregnancy, Brit. M. J. 4462: 51, July 13, 1946.**

This case is reported because of the rarity of the condition, the fact that this type of tumor complicating pregnancy has not previously been reported, and the unusual degree of malignancy. The general incidence is probably about 0.1 per cent of breast tumors and only about one-third of these are malignant.

When three months pregnant, a twenty-year-old primipara noticed a hardness developing in her left breast. When she was admitted to Charing Cross Hospital three months later, the



tumor measured 72 cm. in circumference. Clinical signs of infection were present. Radiation therapy was started. Biopsy was negative for neoplastic cells and aspiration yielded blood. Amputation was decided upon because of anemia, hemorrhage into the tumor, and ulceration. Local recurrence appeared in the scar but resolved with radiotherapy. Recurrences again developed and disappeared with therapy. Delivery was uncomplicated at term and the patient died two months post partum with evidence of metastases. The tumor removed weighed 2,400 Gm., was 75 cm. in circumference, resembled organized blood clot on cross section, and microscopically was classified as an angioblastoma.

R. G. DOUGLAS.

### Malignancies

**Posey, Louis C., and Cunningham, Joseph A.: Impressions of the Vaginal Smear Technic in the Diagnosis of Cervical Cancer, South. M. J. 41: 217, 1948.**

The vaginal smear for the diagnosis of uterine cancer is technically simple but requires considerable time for examination of the smear and skillful interpretation of vaginal cytology. The cancer cell shows a cellular pleomorphism and basophilia which is a function of the rate of cell growth. In slow-growing malignant tumors, these findings may be absent, thus making interpretation difficult. Another note of warning is sounded on the basis that desquamation of tumor cells is a function of surface area and rate of growth and, therefore, cancer with small surface area and slow growth may desquamate sparingly and thus increase the error in diagnosing from the vaginal smear. In acute infection superimposed upon the cancer site, the exudate may dilute the desquamated cells and, being highly cytotoxic, may bring about desquamation of the malignant cells prior to exfoliation. It is felt that the smear method as a satisfactory screen method test for cancer is yet to be established.

WILLIAM BICKERS.

**Speck, George: A Clinical Review of Papillary Adenocarcinoma of the Ovary, Virginia M. Monthly, April, 1948, p. 185.**

Carcinoma of the ovary makes up approximately one-third of all ovarian neoplasms. Thus, the frequency is second only to malignancies arising in the cervix and corpus uteri. Papillary adenocarcinoma is the most common of the malignant tumors of the ovary. Early signs and symptoms are absent, thus bringing most patients to diagnosis late in the disease.

It is thought that the tumors arise from the germinal epithelium covering the ovary. They usually arise bilaterally or, at the time of operation, are usually found bilaterally. Pathologically, the different diagnosis between benign and malignant papillary tumors of the ovary may be quite difficult. Indeed, pathologists do not agree on cytologic criteria for the different diagnosis. The surgeon is left with the responsibility of treating all papillary tumors of the ovary as malignant neoplasms. Radical surgery is necessary because of extensive lymph drainage from the ovary and the tendency of these tumors to metastasize the tubes and uterus. It is generally conceded that the cure must depend almost entirely upon surgery, as radiation therapy offers little in the way of improving the survival rate. Prognosis for the papillary adenocarcinoma is grave. The gross extent of the lesion and the histologic appearance of the tumor influence the survival rate. The best five-year survival thus reported is 50 per cent in a group of patients in whom the lesion was small, limited to one ovary, and apparently removed completely at operation. The overall survival rate for all patients with papillary adenocarcinoma probably does not exceed 5 per cent.

WILLIAM BICKERS.

**Ashworth, C. T., and Diddle, A. W.: Anaplastic Cervical Epithelium, South. M. J. 41: 217, 1948.**

The histologic characteristics of sixteen cervixes with anaplastic epithelium have been studied and compared with those of invasive carcinoma of the cervix. The cervixes which showed anaplasia were found among 1,815 patients upon whom biopsy of the cervix was done. Anaplasia is characterized by hypertrophy, hyperchromatization, and variation in the size of the nuclei. The basement membrane is usually lobulated, although remaining intact. His-

tologically, with the exception of invasion, the anaplastic epithelium is distinguishable from noninvasive carcinoma. Nuclear measurements were done and the nuclear volume for anaplastic and carcinoma cells was similar, both being much greater than that for normal cervical epithelial cells.

It is thought that anaplasia of the cervix may be the precursor of invasive carcinoma. In other studies, follow-up of patients showing these epithelial changes has shown that a high percentage of them develop invasive carcinoma.

WILLIAM BICKERS.

**Hill, Wm. Harry, and Glenn, Wadley R.: Multiple Pelvic Malignancies, South. Surg. 14: 192, 1948.**

Multiple primary malignancy arising in the different organs of the same patient is sufficiently rare to be noteworthy.

A case is reported of a 57-year-old white woman who was admitted with a history of intermittent bloody diarrhea. Examination revealed a normal cervix but the pelvis was frozen and the anterior vaginal fornix filled with a firm fixed mass. Rectal examination revealed a palpable rectal lesion. Diagnosis of pelvic malignancy with obstruction and metastases to the bowel was made. The patient showed signs of intestinal obstruction. At operation, a bilateral pseudomucinous cystadenocarcinoma of the ovary was found, and, at the rectal sigmoid junction, there was a primary annular carcinoma. The pathologic report confirmed the clinical impression that the two malignancies arose independently.

WILLIAM BICKERS.

### Miscellaneous

**Bloxsum, Allan, and Matthaei, Rose: An Anti-Rh Antigen-Antibody Reaction Factor (The Rh Protective Factor), Bull. Johns Hopkins Hosp. 82: 1, 1948.**

In a preliminary article the authors show a factor in the blood of Rh-negative individuals which inhibits the reaction between anti-Rh serum and Rh-positive cells. This is said to be different from blocking antibody. The factor is present in greater strength in Rh-negative males, and the use of their blood in the transfusion of erythroblastotic infants is thought to be therapeutically beneficial. Its use in the prevention of hemolytic disease by transfusion of the mother is suggested.

LOUIS M. HELLMAN.

**Reynolds, S. R. M., Heart, O. O., Bruns, Paul, and Hellman, L. M.: A Multi-Channel Strain-Gage Tokodynamometer: an Instrument for Studying Patterns of Uterine Contractions in Pregnant Women, Bull. Johns Hopkins Hosp., April, 1948.**

An entirely new form of multichannel tokodynamometer using 3 strain gages simultaneously is presented. An electric-spark frictionless recorded portrays graphically the contraction patterns of three different zones of the uterus during labor. Tracings of normal labor are portrayed. These show a substance of activity of the mid zone and lower segment as labor progresses. Toward the end of the first stage, there is a complete preponderance of the fundus. Records portraying the effect of small doses of pituitary extract on normal labor are also shown. The records can be analyzed for frequency, rhythmicity, total relative work per unit period of time, intensity of contraction, contraction time, contraction duration, and contraction and relaxation rates. Because of the construction of the pick-ups, the instrument permits great localization of effect. It is thus possible to demonstrate the gradual emergence of the fundus as the predominating contractile force during labor.

LOUIS M. HELLMAN.

**James, Hal P., Elliott, Henry W., and Page, Ernest W.: Oxygen Uptake of Human Placental Tissue as Affected by Selected Substrates and Drugs, Society for Experimental Biology and Medicine 67: 1948.**

The effects of various drugs on the oxygen uptake of the term human placenta was studied. The CO<sub>2</sub> was depressed by the Demerol, Amytal, scopolamine and diethylstilbestrol. Morphine had no effect. The drug concentrations used were all in excess of the therapeutic dosage.

LOUIS M. HELLMAN.

### Newborn

**Franklin, Charles H.: Penicillin in Drops for Prophylaxis Against Ophthalmia Neonatorum, South. M. J. 41: 320, 1948.**

A single instillation of penicillin in the conjunctival sac in the prophylaxis against ophthalmia neonatorum is evaluated. A total of 1,107 infants was studied in the nursery and in the home during the first two weeks of life. 1.1 per cent of the infants exhibited a purulent discharge in the eyes. This percentage is approximately one-sixth of that observed following the use of silver nitrate.

In the thirteen infants who exhibited a purulent discharge during their hospitalization, culture was taken in all and fifteen different organisms were isolated from the thirteen cultures. Two-thirds of the isolated organisms were staphylococci. A follow-up study was made on 952 infants (80.9 per cent) after the patients had returned to their homes, on the fourteenth and seventeenth days of life. Of these, 902 infants were reported by the Public Health Nurse as having no ophthalmic signs. The others showed evidence of conjunctival redness or watery discharge. Of those showing purulent discharge on follow-up examination, cultures were obtained in twenty-one infants and organisms were found in all except one. The total incidence of purulent discharge in the hospitalized group was 1.1 per cent on the penicillin prophylaxis as compared to 6 per cent with silver nitrate prophylaxis.

WILLIAM BICKERS.

**Salmon, George W.: Airblock in the Newborn Period, New Orleans M. & S. J. 100: 253. 1947.**

Airblock is a term used to designate extrapulmonary vesicular air. Too often, death occurring in the neonatal period is attributed to small areas of atelectasis, though it is well known that several days are required for complete expansion of the newborn lung. There are good reasons for believing that aberrant air which is a common cause of neonatal death is often overlooked at necropsy. Although emphysema in the mediastinum is readily detected, air in the pulmonary vesicular areas of the lung is less readily identified. Escape of air is likely to take place when alveoli are overinflated without corresponding increase in the circumference of the underlying vessels. Artificial respiration, particularly with positive pressure machines, can be a factor in forcing air through the alveoli. Occasionally the rupture extends to the pleura, producing a pneumothorax. More often the interstitial air travels along the pulmonary vessels to the mediastinum. From here it occasionally can extend to the cervical subcutaneous tissue.

The outstanding symptoms of airblock are dyspnea and cyanosis, reduction of the respiratory excursion with greatly increased rate, distention of the neck veins, heart sounds faint and distant; pain is symptomatic of the adult but is difficult to evaluate in the newborn. Treatment is unsatisfactory unless pneumothorax occurs, when air can be moved by needle. Excellent photomicrographs illustrate the article.

WILLIAM BICKERS.

### Pregnancy, Complications

**Palmer, Lester J., Crampton, Joseph H., and Barnes, Robert H.: Pregnancy in the Diabetic, West. J. Surg. 56: 175, 1948.**

Following the report by Priscilla White on the improved fetal survival in diabetics by the use of ovarian sterile therapy, the authors adopted her treatment program. They had previously reported, in 1945, 68 pregnancies observed in 48 diabetic women treated with hormone therapy other than insulin, and now they took 39 diabetic women treated with stilbestrol and progesterone. In the first group, the over-all fetal survival rate was 60 per cent. The second series treated with varying dose schedules of progesterone and stilbestrol had a fetal survival rate of 76.9 per cent. There was no maternal mortality in either series.

Stilbestrol and progesterone therapy was started in the sixteenth week of gestation. Progesterone was given in a dose of 10.0 mg. two times per week and the dose increased until, at the thirty-second week, the patient was receiving 15 mg. daily. Approximately 25 mg. of stilbestrol were given daily from the sixteenth week until delivery. Hormone requirements and the effect of therapy were not checked by pregnandiol excretion studies or serum gonadotropin levels.

It is believed that all diabetic women should be delivered by the end of the thirty-sixth week of gestation. If spontaneous delivery does not occur, cesarean section is a procedure of choice.

WILLIAM BICKERS.

**Matthew, G. D.: Thrombophlebitis in Pregnancy, Edinburgh M. J. 54: 641-48, 1947.**

Pregnancy phenomena predisposing to thrombophlebitis are (a) elevated plasma fibrinogen, (b) venous stasis in the legs (especially with the large uteri of hydramnios or multiple pregnancy), (c) the occasional need for long periods of antepartum bed rest, (d) trauma to leg veins during labor and delivery, and (e) bacterial invasion of the physiologic thrombi in the placenta site sinuses. The incidence of thrombophlebitis is high (4 per cent) after cesarean section and difficult forceps deliveries.

In 19 cases treated with heparin, hospitalization was a week shorter than in a control series. The author suggests early exercises, massage, and heparinization as prophylaxis in predisposed women.

IRVING L. FRANK.

### Pregnancy, Physiology

**Hickey, M. D., and de Valera, E.: Variation in the Titre of Rh Antibody During Pregnancy, Brit. M. J. 4497: 335, 1947.**

The authors record the antibody titer as determined by the conglutination method of Wiener before, and at frequent intervals during, the sixth pregnancy of an Rh-negative patient with one living child. The figures indicate that a rise in antibody titer occurred during early pregnancy followed by a fall which was attributed to absorption of the antibody by the Rh-positive fetus. Following delivery by cesarean section at the thirty-second week, there was an immediate rise in the antibody titer from 1:16 to 1:256. The baby died twelve hours after delivery despite transfusions. Blood films showed a definite erythroblastosis.

R. G. DOUGLAS.

### Pregnancy, Toxemia

**Bracciale, U.: Circulating Neutrophile Stabform in Toxemias of Pregnancy, Archivio di Ostetricia e Ginecologia 53: 31, 1948.**

In the healthy state, only mature segmented forms of neutrophile leucocytes enter the peripheral blood; the immature stab or band form described by Schilling is an occasional finding.

Segmented forms, the mature form of neutrophiles, account normally for 60 to 70 per cent of the circulating leucocytes, and the ratio of the juvenile form, the band form in which nuclear width is approximately uniform through the entire length of the nucleus, to the mature segmented form, is in normal cases as low as 0.05 to 0.06.

Bracciale at the Lying-in Hospital in Naples examined the ratio of band-form to mature cells in 20 cases of toxemias of pregnancy in the puerperium: 12 cases of eclampsia; 6 of pre-eclampsia; 2 of abruption of a normally inserted placenta.

The ratio showed normal values in six cases. It was increased in fourteen cases. No correlation was found between severity of the toxemia and number of circulating immature neutrophiles. In three cases, however, in which the puerperium was complicated by infection,



and penicillin and sulfonamide treatment was instituted, the band to segmented ratio reached a value of 0.97, and in two cases of puerperal eclampsia regressive features such as vacuolization concentration of the chromatin, and pyknosis were present.

These findings point to the presence of an increased stimulation of the bone marrow during pregnancy.

GEMMA BARZILAI.

### Radiation

**Del Regato, J. A.: The Role of Transvaginal Roentgentherapy in the Treatment of Carcinoma of the Cervix, Surg., Gynec. & Obst., April, 1948.**

The author reports the use of a special speculum and moderately low voltage x-ray in the transvaginal treatment of carcinoma of the cervix. He claims a lower incidence of complications if this method is used as an adjunct to external pelvic irradiation. In 76 patients with all types of cervical carcinoma there was a 44 per cent three-year survival.

LOUIS M. HELLMAN.

**Kaplan, Henry S., Wilson, Hugh M., and Morse, Arthur H.: Results and Causes of Failure of Radiation Therapy in Carcinoma of the Cervix, Surg., Gynec. & Obst., March, 1948.**

A small series of 88 patients with carcinoma of the cervix, treated with combined x-ray and radium, is reviewed. There is a total 38 per cent five-year survival with a 61 per cent salvage in stage I. While this compares favorably with other reports, the survival rates in stages III and IV were very low.

LOUIS M. HELLMAN.

### Sterility, Fertility

**Hoffman, Eugene F.: Semen Evaluation and Fertility, West. J. Surg. 56: 155, 1948.**

A fertile semen specimen has the following characteristics: alkaline reaction, at least 3 c.c. in volume, grade 3 or better in motility, 60,000,000 or more per c.c., and 20 per cent or less in abnormal form. There are very few pus cells and no red blood cells in the normal specimen. There are summarized the observations made upon 495 patients.

Of this group, 27 per cent met the requirements for a normal seminal fluid described above, whether or not treated. Eighteen per cent were found to be relatively infertile but refused treatment. The remaining 55 per cent underwent treatment. In the group, there were 22 per cent who, on two or more examinations, had azoospermia which did not respond to any type of treatment. Thirteen of this group had an obstructed vas, eight had atrophic testes following mumps, and in the remaining patients no pathology could be demonstrated. In the group whose specimens showed only relative infertility, there were 35 who were still infertile when treatment was stopped, 46 who showed no improvement in the treatment, and 76 who showed improvement but were not able to impregnate their wives. There were 57 of the 495 patients who succeeded in impregnation, one of these with a seminal count which never exceeded 2,000,000 per c.c. A relatively large number of the patients with defective seminal fluid had seen military service in the South Pacific where heat, humidity, exhaustion, and poor food would seem to be the contributing factors. Many men, however, associated their infertility with having been in proximity to radar equipment. There was no evidence to support this assumption.

WILLIAM BICKERS.

## Correspondence

### Stilbestrol in Endometriosis

*To the Editor:*

In the section under correspondence of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, I read a letter on endometriosis by Lowell F. Bushnell of Los Angeles.

At the time that the editorial appeared a paper was being prepared on the use of stilbestrol (estrogen) for treatment of endometriosis. Dr. Bushnell states that whenever diagnosis of endometriosis is proved "... the patient be instructed never to have estrogen therapy." From our studies on endometriosis in the past ten years at Jefferson Davis Hospital we have never been able to cause endometriosis to be worse by giving large doses of stilbestrol. Stilbestrol was given in three cases of endometriosis of the incision and in three cases of endometriosis of the posterior cul-de-sac. In all cases given stilbestrol, the blue nodule disappeared and became white and hard. After stilbestrol was discontinued for twelve, eight, six, and three months, there was no recurrence of blueness or bleeding from these endometrial areas. All patients are now menstruating normally with little or no pain.

Stilbestrol has been given to approximately 60 patients with endometriosis associated with severe pains before and during menstruation, now with most gratifying results and I have never seen a case made worse. One patient had a large endometrial implant in the posterior cul-de-sac. A biopsy was taken before therapy and approximately every 30 days for four times. She was given stilbestrol, 5 mg. daily increasing 5 mg. weekly for three and one-half months. The last biopsy revealed no endometriosis. If stilbestrol caused endometriosis to become worse, then in this case endometriosis would have been present in all subsequent biopsies. Yet no endometriosis was found in any of the subsequent sections. Culdesopic examination with a Decker's instrument revealed no pelvic endometriosis. Pelvic organs which were stuck and painful became freely movable. In another case, pelvic endometriosis was diagnosed by laparotomy and biopsy. She again had all signs and symptoms of endometriosis at approximately three months after operation. Large and increasing doses of stilbestrol were given and in four to six weeks the pelvic organs became freely movable. Stilbestrol was discontinued and menstruation began which was many times less painful. She became pregnant in about three months after stilbestrol was discontinued.

One patient with endometriosis in the posterior cul-de-sac, which was seen grossly, had been married for eleven years and had no children. She became pregnant two months after stilbestrol was discontinued.

In another case, the uterus had ruptured with resulting endometriosis eight years ago. Large doses of stilbestrol were given and she has also become free of pain which was associated with endometriosis.

A patient had one child 7 years ago and presented all signs and symptoms of endometriosis. An operation had been suggested. She was given stilbestrol up to 100 mg. daily for three months. After discontinuing stilbestrol the pelvic organs became freely movable. She is now eight months pregnant.

0.1 to 25 mg. of stilbestrol were given to 20 endometriotic cases and it caused the pain to be worse.

It might be assumed that within the next ten years stilbestrol will assume one of the most important roles in the treatment of endometriosis and might replace x-ray, surgery, and radium in 75 per cent of endometriotic cases.

One may give small doses of codeine in mild cases of endometriosis and eliminate the mild pain, but it is known that endometriosis, as a rule, grows and grows so that such therapy may give one false security and resulting more extensive endometriosis at a later date. Stilbestrol appears to be a more rational therapy for mild or severe endometriosis.

KARL JOHN KARNAKY, M.D.

HOUSTON, TEXAS.

June 23, 1948.

### Condylomata Acuminata

*To the Editor:*

A pregnant woman had verruca acuminata (condylomata acuminata). As treatment she was given two injections of neoarsphenamine. Subsequently she developed encephalopathy and came under the management of Kantor and Levin. Their diagnosis was arsenical encephalopathy (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, August, 1948). Seven months after delivery the patient still had distressing neurological residuals.

A simple painless cure for condylomata acuminata is to paint them with a 25 per cent suspension of podophyllin in castor oil. This will cause the growths to disappear completely in several applications (depending on their extent) leaving the skin unaffected. However, the medicine must be applied to the growths only and not to the surrounding skin.

This treatment which deserves to be better known is superior to excision or cauterization under local or general anesthesia. It is certainly superior to the many nonsurgical remedies, such as application or injection of this or that substance (see any textbook) which turns out on trial to be questionable or worthless.

CHESTER D. BRADLEY, M.D.

2914 WEST AVENUE,  
NEWPORT NEWS, VA.  
AUG. 21, 1948.

---

### Erratum

In the article, "The Hydrostatic Bag in Obstetrics," by N. S. Assali and R. W. Kistner, in the October issue of the JOURNAL, on page 787, in Table VI, at the top of the page, the words "Dilatation" and "Bleeding" are reversed. "Bleeding" should precede the first line of figures, and "Dilatation," the second.

## Necrology

---

JENNINGS CRAWFORD LITZENBERG, B.A., M.D., a member of the Advisory Board of the JOURNAL since its founding, professor emeritus and former head of the Department of Obstetrics and Gynecology at the University of Minnesota, author and teacher, died at the age of 78 years at his home in Minneapolis, from coronary occlusion, on Aug. 15, 1948. Dr. Litzenberg was prominent in the development of maternity care in the upper midwestern states, a member of the national and local medical societies, a past president of the American Gynecological Society, faculty counselor for twenty years of the Alpha Omega Alpha Fraternity, and a founder of the Minnesota Medical Foundation.

---

GEORGE L. STREETER, M.D., former director of the Department of Embryology of the Carnegie Institute of Washington and noted for his many contributions in this field, died of a heart attack in July, 1948, at the age of 75 years.

Dr. Streeter was graduated from the College of Physicians and Surgeons of Columbia University in 1899, served on the faculty of the Wistar Institute, Philadelphia, and then as professor of anatomy at the University of Michigan from 1907 to 1914. Coming to the Carnegie Institute, he developed the world-renowned collection of human embryologic material and wrote extensively for many publications.



## Items

---

### American Board of Obstetrics and Gynecology

The following physicians are to be included in the list of diplomates certified by this Board:

Brown, Hunter Merrill, 1922 South Tenth Avenue, Birmingham, Alabama, born 1909, received M.D. from Tulane University in 1934.

Magee, Thomas Lea, II, 578 Polk Street, Monterey, California, born 1908, received M.D. from Stanford University in 1939.

Stowe, Lyman M., New Haven Hospital, New Haven, Connecticut, born 1914, received M.D. from Yale University in 1938.

PAUL TITUS, M.D., Secretary.

---

### American Board of Obstetrics and Gynecology, Inc.

A number of changes in Board requirements and regulations were made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22, 1948. New Bulletins are now available for distribution upon application and give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

Foremost are the following:

(1) The ruling that applicants must receive adequate training in both obstetrics and gynecology has been defined as meaning a minimum of six months, full-time, in the branch of either obstetrics or gynecology relegated to a minor role in a candidate's training and preference for practice.

(2) Acceptable preceptorship training is defined.

(3) The present regulation requiring at least six months of practice in the specialty following the completion of an acceptable training period, has now been extended, effective Dec. 31, 1949, to a requirement of two years post-training practice limited to the specialty.

(4) Specific requirements for approval of hospital services for residency training are outlined.

(5) Effective immediately, there will be no further temporary approvals of hospital services for residency training. It is planned that all hospitals holding any type of residency training approval will soon either be resurveyed or initially surveyed by the Council on Medical Education and Hospitals of the A. M. A. so that all future approvals, new or old, will be based entirely upon inspection following application. It is expected also that certain resurveys will result in withdrawal of present residency approval from institutions where the educational and training standards are not being maintained.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 4, 1949. Application may be made until Nov. 1, 1948. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,  
1015 HIGHLAND BUILDING,  
PITTSBURGH 6, PA.

### American Urological Association

The American Urological Association offers an annual award of \$1000.00 (first prize of \$500.00, second prize \$300.00 and third prize \$200.00) for essays on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Biltmore Hotel in Los Angeles, May 16-19, 1949.

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tenn. Essays must be in his hands before February 15, 1949.

### The Twelfth British Congress of Obstetrics and Gynaecology

To be held in the Friends Meeting House, Euston Road, London, in July, 1949.

*President:* Sir Eardley Holland. } 58, Queen Anne Street,  
*Hon. Secretaries:* A. Joseph Wrigley. } (Royal College of Obstetricians & Gynaecologists)  
Ian Jackson. } London, W.1.

WEDNESDAY, July 6.

*Morning Session.*—(Chairman: The President)

The Congress will be declared open by the Minister of Health.

“Modern Caesarean Section.” Introduced by Mr. McIntosh Marshall (Liverpool).

*Afternoon Session.*—

(1) Guest Paper. Dr. Joe Meigs (Boston, Mass.).

(2) “Pregnatediol.” Introduced by Prof. C. F. Marrian (Edinburgh) and Dr. G. I. M. Swyer (London).

THURSDAY, July 7.

*Morning Session.*—

“Essential Hypertension in Pregnancy.” Introduced by Prof. George Pickering (London) and Prof. F. J. Browne (London).

*Afternoon Session.*—

(1) “Hernia of Pouch of Douglas.” Introduced by Mr. Charles Read (London).

(2) “The Management of Pregnancy in Diabetics.” Introduced by Mr. John Peel (London) and Prof. D. M. Dunlop (Edinburgh).

FRIDAY, July 8.

*Morning Session.*—

“Diagnosis and Prognosis of Carcinoma of the Uterus.” Introduced by Dr. J. E. Ayre (Montreal), and Dr. Spears (Cambridge).

*Afternoon Session.*—

Discussion on Maternal Mortality.

Owing to the difficulties that exist at the present time in arranging hotel accommodation, travel, etc., the Hon. Secretaries would like to have the names of those who hope to attend, by March 31, 1949, at the latest, and, if possible, very much before that date.